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(54) **Novel quinoline carboxylic acid derivatives having 7-(4-amino-methyl-3-oxime) pyrrolidine substituents and processes for their preparation**

(57) The present invention relates to a novel quinolone compound having an excellent antibacterial activity. More specifically, the present invention relates to a novel quinoline(naphthyridine)carboxylic acid derivative represented by the following formula (I), which has an 4-aminomethyl-3-oximepyrrolidine substituent on 7-position of the quinolone nucleus and shows a superior antibacterial activity in contrast to the known quinolone antibactrial agents having a weak activity against gram-positive bacterial strains and also has a broad antibacterial spectrum and a highly improved pharmacokinetic property :

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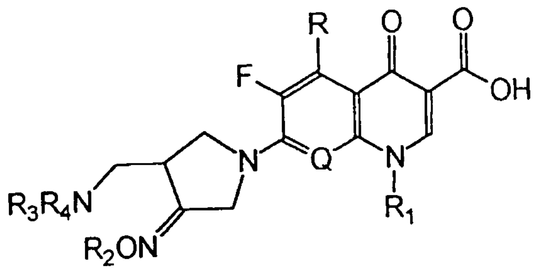


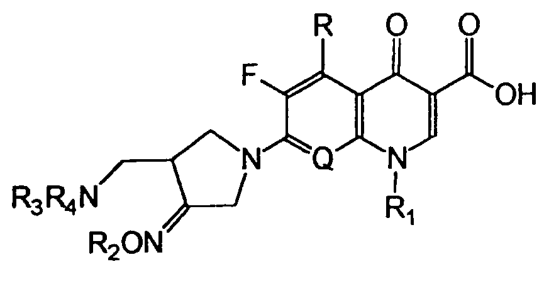
(I)

wherein R, R_1, R_2, R_3, R_4 and Q are defined as described in the specification.

BACKGROUND OF INVENTION

1. Field of Invention

The present invention relates to a novel quinoline(naphthyridine) carboxylic acid derivative having an excellent antibacterial activity. More specifically, the present invention relates to a novel quinoline-(naphthyridine)carboxylic acid derivative represented by the following formula (I), which has an 4-aminomethyl-3-oximepyrrolidine substituent on 7-position of the quinolone nucleus and shows a superior antibacterial activity in contrast to the known quinolone antibacterial agents and also has a broad antibacterial spectrum and a highly improved pharmacokinetic property:



(I),

and its pharmaceutically acceptable non-toxic salt, its physiologically hydrolyzable ester, solvate and isomer, in which

R represents hydrogen, methyl or amino;

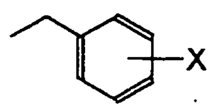
Q represents C-H, C-F, C-Cl, C-OH, C-CH_3, C-O-CH_3 or N;

R_1 represents cyclopropyl, ethyl, or phenyl which is substituted with one or more fluorine atom(s);

R_2 represents one of the following a) through e):

a) hydrogen, straight or branched C_1-C_4 alkyl, cyclopropyl, cyclopropylmethyl, C_3-C_6 alkynyl, 2-haloethyl, methoxymethyl, methoxycarbonylmethyl, aryl or allyl,

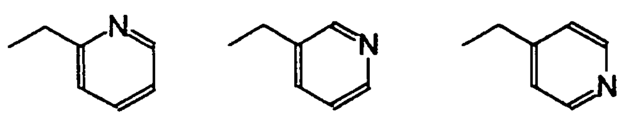
b) a group of the following formula (1),



(1)

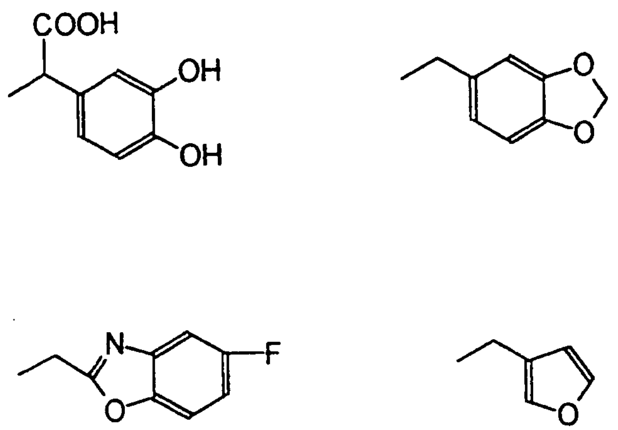
wherein X represents hydrogen, 2, 3 or 4-fluoro, cyano, nitro, methoxy, C_1-C_4 alkyl, or 2,4-difluoro,

c) a group of the following formula (2),



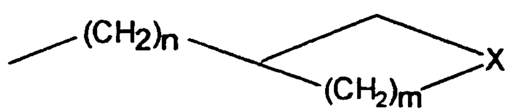
(2)

d) a heteroarylmethyl of the following formula (3),



(3)

e) a group of the following formula (4),



(4)

wherein n denotes 0 or 1, m denotes 0, 1 or 2, and X represents methylene, O or N, and

R_3 and R_4 independently of one another represent hydrogen or C_1-C_3 alkyl or R_3 and R_4 together with a nitrogen atom to which they are attached can form a ring.

The present invention also relates to a process for preparing the compound of formula (I), as defined above, and an antibacterial composition comprising the compound of formula (I) as an active component.

2. Background Art

Since in 1962 nalidixic acid was first introduced as an agent for treating urinary tract infection (see, G. Y. Lesher, et al., J. Med. Chem. 5, 1063-1065 (1962)), numerous quinoline carboxylic acid antibacterial agents, including oxolinic acid, rosoxacin, pipemidic acid, etc., have been developed. However, these early-stage antibaterial agents have a little activity against gram-positive bacterial strains and thus have been used only against gram-negative strains.

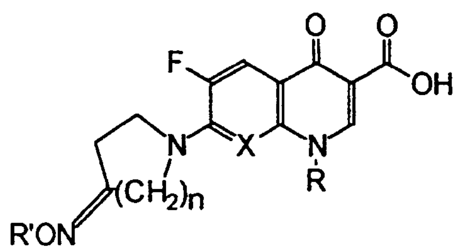
Recently, norfloxacin which is the quinolone compound having a fluorine on 6-position has been newly developed (see, H. Koga, et al., J. Med. Chem., 23, 1358-1363 (1980)), and thereafter an extensive study to develop various quinolone antabacterial compounds has been conducted. However, since norfloxacin has a weak antibacterial activity against gram-positive strains and shows poor distribution and absorption in living body, it has been used only for treatment of diseases including urinary tract infections, gastro-intestinal infections, sexually transmitted diseases and the like. Thereafter, ciprofloxacin (see, R. Wise, et al., J. Antimicrob. Agents Chemother., 23, 559 (1983)), ofloxacin (see, K. Sata, et al., Antimicrob. Agents Chemother., 22, 548 (1982)) and the like have been developed. These antibacterial agents have a superior and broad antibacterial activity in comparison with the early-stage antibacterial compounds, and therefore, have been widely and practically used for treatment of diseases in clinical field.

The compounds in use or under clinical test include mainly the derivatives having a piperazine substituent on 7-position of the quinolone nucleus as in ciprofloxacin or ofloxacin. However, as a result of the study to develop quinolone compounds having a more potent and broad antibacterial activity it has been disclosed that a compound having an 3-amino or 3-aminomethylpyrrolidine group introduced into 7-position has an increased activity against gram-positive strains, in comparison with the compounds having 7-piperazine group, while maintaining a potent activity against gram-negative strains. However, unfortunately, the compounds having pyrrolidine substituent have a low solubility in water in comparison with the compounds having piperazine substituent, and thus their in-vivo antibacterial activity is not so high as the

in-vitro activity. Accordingly, numerous study has been continuously conducted to improve the disadvantage of the compounds having pyrrolidine substituent, that is, to increase the solubility in water and to improve the pharmacokinetic property.

As a result, many reports of such study have been made. For example, it has been disclosed that ((2S, 4S)-4-amino-2-methylpyrrolidinyl)naphthyridine derivatives (see, Rosen, T., Chu, D. T. W. etc. J. Med. Chem. 1988, 31, 1598-1611) or (trans-3-amino-4-methylpyrrolidinyl)naphthyridine derivatives (see, Matsumoto, J. et al., Proceedings of the 14th International Congress of Chemotherapy; Ishigami, J., Ed.; University of Tokyo Press: Tokyo, 1985; pp 1519-1520) shows a 20 to 40 times increase in water-solubility, an increased bioavailability and an improved pharmacokinetic property, in comparison with the compounds having no methyl group, with a similar in-vitro antibacterial activity.

In addition, an attempt to improve the disadvantage of the prior quinolone compounds including a relatively low antibacterial activity against gram-positive strains, a low water-solubility and a poor pharmacokinetic property has been made by introducing different functional groups, instead of amino group, into the pyrrolidine or piperazine moiety. As one of such attempt, some compounds having an oxime group introduced into the 7-amine moiety of quinolone compounds have been reported. For example, the researchers of Abbott have reported in a scientific journal, J. Med. Chem., 1992, 35, 1392-1398, that the quinolone compound having the following general formula [A] wherein 3-oxime(or methyloxime)pyrrolidine group or 4-oxime(or methyloxime)piperidine group is substituted on 7-position of quinolone nucleus exhibits a good antibacterial activity against gram-positive strains:



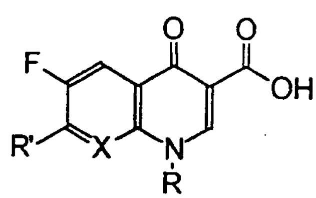
[A]

in which

- R represents cyclopropyl or 2,4-difluorophenyl;
- R' represents hydrogen or methyl;
- X represents C-H, C-F or N; and
- n denotes 1 or 2.

The compound [A] has some disadvantages that it shows a good antibacterial activity against gram-positive strains but a relatively weak activity against gram-negative strains, and also has a relatively low antibacterial activity in in-vivo test.

In addition, Japanese Laid-open Patent Publication No. (Hei) 01-100165 (1989) discloses the compound having the following general formula [B]:



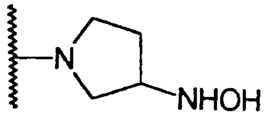
[B]

in which

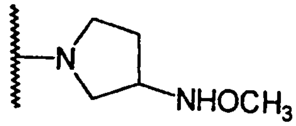
- R represents cyclopropyl, 2,4-difluorophenyl or 4-hydroxyphenyl;
- X represents C-H, C-F or C-Cl; and
- R' represents oxime or hydroxyaminopyrrolidine-derived substituent.

Specifically, in said Japanese laid-open publication the oxime or hydroxyaminopyrrolidine-derived groups as R' substituent are very broadly disclosed. However, only the 3-hydroxyaminopyrrolidine [the following formula (a)], 3-methoxyaminopyrrolidine [the following formula (b)], 3 amino-4-methoxyaminopyrrolidine [the following formula (c)], 3-oximepyrrolidine [the following formula (d)] and 3-methyloximepyr-

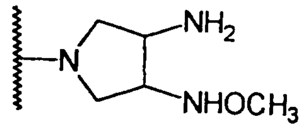
rolidine [the following formula (e)] groups are specifically exemplified but the pyrrolidine substituent having both 3-oxime and 4-aminomethyl groups has never been specifically mentioned.



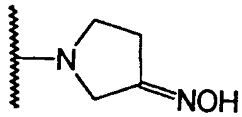
[a]



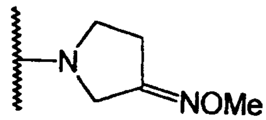
[b]



[c]

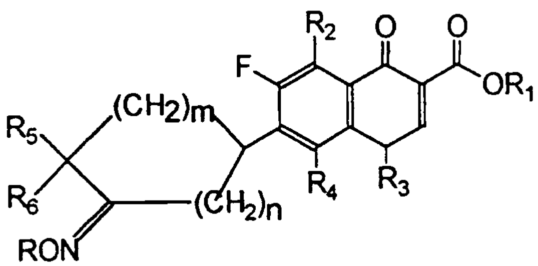


[d]



[e]

Further, European Early Patent Publication No. 0 541 086 discloses the quinolone compound having the following general formula [C]:

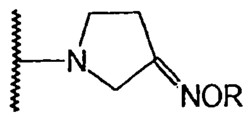
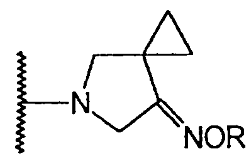


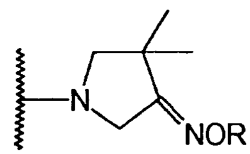
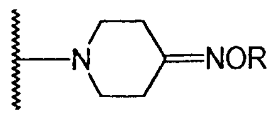
[C]

in which

R and R_1	independently of one another represent hydrogen or C_1-C_5 alkyl;
R_2	represents hydrogen, amino, fluoro or hydroxy;
R_3	represents C_3-C_7 cycloalkyl;
R_4	represents methoxy or fluoro;
R_5 and R_6	can be identical with or different from each other and independently of one another represent hydrogen or alkyl, or R_5 and R_6 together can form C_3-C_5 cycloalkyl;
m	denotes 0 or 1; and
n	denotes an integer of 1 to 3.

Among the compounds [C] disclosed in said European early patent publication the typical substituent on 7-position of quinolone nucleus is a group having the following structure:

However, the compound of formula [C] does not include any compound having both oxime group and aminomethyl group on 7-position, and therefore, is different from the compound of the present invention.

The common characteristic feature of the known oxime or hydroxyamine-derived compounds as mentioned above is that they exhibit a good activity against gram-positive strains including MRSA (Methicillin Resistant Staphylococcus aureus) strains in comparison with the early developed quinolone compounds but show a weak activity against gram-negative strains in comparison with the antibacterial agents including ofloxacin or ciprofloxacin. Therefore, it can be said that their antibacterial spectrum may be narrower than that of the known ofloxacin or ciprofloxacin antibacterial compound.

Thus, on the basis of prior art as mentioned above the present inventors have extensively studied to develop the novel oxime-aminomethyl compound, which shows a potent antibacterial activity against broad spectrum pathogenic strains including resistant strains and also exhibits more improved pharmacokinetic properties and high absorption in living body, by introducing various substituted pyrrolidine groups into 7-position of quinoline nucleus and determining pharmacological activities of the resulting compounds. As a result, we have identified that the quinolone compounds having the general formula (I), as defined above, wherein 4-aminomethyl-3-(optionally substituted)oxime-pyrrolidine group is introduced into 7-position of quinoline nucleus can satisfy such purpose, and thus completed the present invention.

Therefore, it is an object of the present invention to provide a novel quinoline(naphthyridine) carboxylic acid derivative of formula (I), as defined above, which shows a potent antibacterial activity against broad pathogenic strains including both gram-positive and gram-negative strains and also has a good pharmacokinetic property.

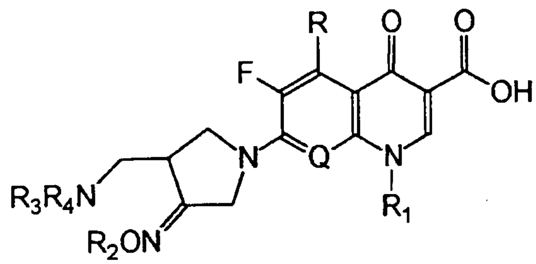
It is another object of the present invention to provide a process for preparing the novel quinoline-(naphthyridine) carboxylic acid derivative of formula (I).

It is a further object of the present invention to provide an antibacterial composition comprising the novel quinoline (naphthyridine)carboxylic acid derivative of formula (I) as an active component.

The foregoing has outlined some of the more pertinent objects of the present invention. These objects should be construed to be merely illustrative of some of the more pertinent features and applications of the invention. Many other beneficial results can be obtained by applying the disclosed invention in a different manner or modifying the invention within the scope of the disclosure. Accordingly, other objects and a more thorough understanding of the invention may be had by referring to the disclosure of invention, in addition to the scope of the invention defined by the claims.

DISCLOSURE OF INVENTION

In one aspect, the present invention relates to a novel quinoline(naphthyridine) carboxylic acid derivative having the following formula (I):



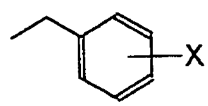
(I)

and its pharmaceutically acceptable non-toxic salt, its physiologically hydrolyzable ester, solvate and isomer, in which

- R represents hydrogen, methyl or amino;
- Q represents C-H, C-F, C-Cl, C-OH, C-CH_3, C-O-CH_3 or N;
- R_1 represents cyclopropyl, ethyl, or phenyl which is substituted with one or more fluorine atom(s);
- R_2 represents one of the following a) through e):

a) hydrogen, straight or branched C_1-C_4 alkyl, cyclopropyl, cyclopropylmethyl, C_3-C_6 alkynyl, 2-haloethyl, methoxymethyl, methoxycarbonylmethyl, aryl or allyl,

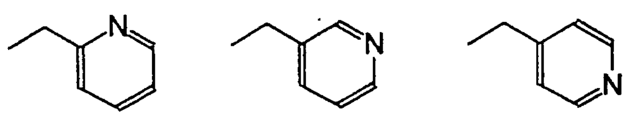
b) a group of the following formula (1),



(1)

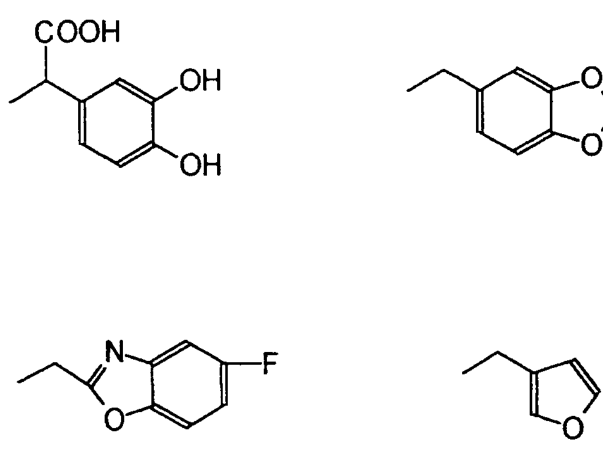
wherein X represents hydrogen, 2, 3 or 4-fluoro, cyano, nitro, methoxy, C_1-C_4 alkyl, or 2,4-difluoro,

c) a group of the following formula (2),



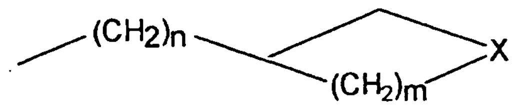
(2)

d) a heteroarylmethyl of the following formula (3),



(3)

e) a group of the following formula (4),



(4)

wherein n denotes 0 or 1, m denotes 0, 1 or 2, and X represents methylene, O or N, and

R_3 and R_4 independently of one another represent hydrogen or C_1-C_3 alkyl or R_3 and R_4 together with a nitrogen atom to which they are attached can form a ring.

Among the compound of formula (I), as defined above, having a superior antibacterial activity, a broad antibacterial spectrum and an excellent pharmacokinetic property, the preferred compounds include those wherein Q represents C-H, C-F, C-Cl, C-OMe or N, R represents hydrogen or amino, R_1 represents cyclopropyl or 2,4-difluorophenyl, R_2 represents hydrogen, methyl, ethyl, isopropyl, t-butyl, phenyl, propargyl, homopropargyl, 2-fluoroethyl, benzyl, 2-fluorobenzyl or 2-cyanobenzyl, and R_3 and R_4 represent hydrogen.

More preferred compounds of formula (I) include those wherein Q represents C-H, C-Cl, C-F or N, R represents hydrogen or amino, R_1 represents cyclopropyl, R_2 represents methyl, t-butyl, homopropargyl, 2-fluoroethyl, benzyl or 2-fluorobenzyl, and R_3 and R_4 represent hydrogen.

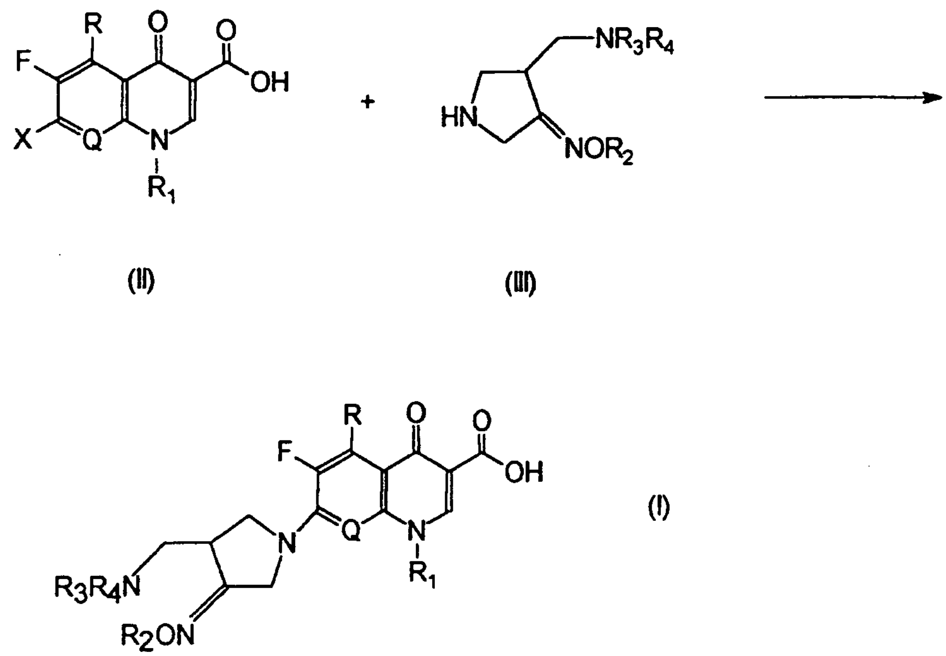
In the pyrrolidine moiety of the compound of formula (I) the 4-carbon atom on which aminomethyl group is substituted is an assymetric carbon atom and thus can be present in the form of R or S or a mixture of R abd S. In addition, due to the presence of (optionally substituted) oxime group on 3-position of pyrrolidine moiety the compound of formula (I) can be present in the form of syn- and anti-isomers depending on their geometric structure. Thus, the present invention also includes all of those geometric isomers and their mixtures.

The compound of formula (I) according to the present invention can form a pharmaceutically acceptable non-toxic salt. Such salt includes a salt with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, etc., a salt with organic carboxylic acids such as acetic acid, trifluoroacetic acid, citric acid, maleic acid, oxalic acid, succinic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, ascorbic acid or malic acid or with sulfonic acids such as methanesulfonic acid, para-toluenesulfonic acid, etc., and a salt with other acids which are generally known and conventionally used in the technical field of quinolone-based compounds. These acid-addition salts can be prepared according to a conventional conversion method.

In the second aspect, the present invention also relates to a process for preparing the novel compound of formula (I).

According to the present invention, the compound of formula (I) can be prepared by reacting a compound of formula (II) with a compound of formula (III) or a salt thereof, as shown in the following reaction scheme 1.

Reaction Scheme 1



In the above scheme,

R, R_1, R_2, R_3, R_4 and Q are defined as previously described; and

X represents a halogen atom, preferably chlorine, bromine or fluorine.

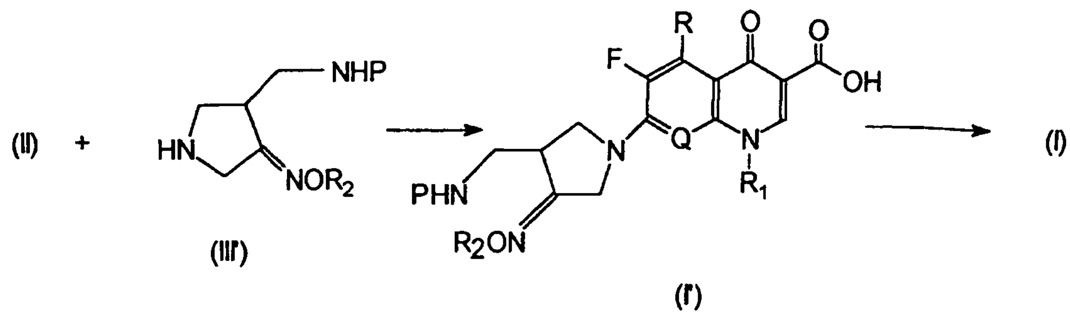
According to the above reaction scheme 1, the compound of formula (I) according to the present invention can be prepared by stirring the compound of formula (II) and the compound of formula (III) in the presence of a solvent for 1 to 20 hours at the temperature between room temperature and 200°C with the addition of a suitable base. In this reaction, the compound of formula (III) can be used in the form of a free compound or a salt with an acid such as hydrochloric acid, hydrobromic acid or trifluoroacetic acid.

As the solvent for the above reaction, any solvent which does not adversely affect the reaction can be used. Preferably, acetonitrile, dimethylformamide(DMF), dimethylsulfoxide(DMSO), pyridine or hexamethylphosphoramide(HMPA) can be used.

This reaction is generally conducted in the presence of an acid acceptor. In this case, to increase the reaction efficiency of the relatively expensive starting material (II) the reactant (III) is used in an excessive amount, for example, an equimolar amount to 10 times molar amount, preferably an equimolar amount to 5 times molar amount, with respect to the starting material (II). When the reactant (III) is used in an excessive amount, the unreacted compound of formula (III) which is retained after the reaction can be recoverd and reused in another reaction. The acid acceptor which can be preferably used in this reaction includes inorganic bases such as sodium hydrogen carbonate, potassium carbonate, etc., and organic bases such as triethylamine, diisopropylethylamine, pyridine, N,N-dimethylaniline, N,N-dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU), 1,4-diazabicyclo[2.2.2]octane(DABCO), etc.

The compound of formula (I) according to the present invention can also prepared by a method depicted in the following reaction scheme 2, in which a protecing group P is introduced into one of R_3 and R_4 of the compound of formula (III) wherein R_3 and R_4 are hydrogen to prepare the compound of formula (III') wherein the amino group is protected with P, the protected compound of formula (III') is reacted with the compound of formula (II) under the same condition as in the reaction scheme 1, and then the resulting compound of formula (I') is deprotected by removing the protecting group P to form the desired compound of formula (I).

Reaction Scheme 2



In the above reaction scheme,

R, R_1, R_2 and Q are defined as previously described; and

P represents an amino-protecting group.

In the reaction of the above reaction scheme 2, the compound of formula (III') can be used in the form of a free compound or a salt with hydrochloric acid, hydrobromic acid or trifluoroacetic acid, as in the compound of formula (III) used in the reaction scheme 1.

Any protecting group which is conventionally used in the field of organic chemistry and can be readily removed after the reaction without decomposition of the structure of the desired compound can be used as the suitable amino-protecting group P in the compound of formula (III'). The specific example of protecting groups which can be used for this purpose includes formyl, acetyl, trifluoroacetyl, benzoyl, para-toluenesulfonyl, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, benzyloxycarbonyl, para-methoxybenzyloxycarbonyl, trichloroethoxycarbonyl, beta-iodoethoxycarbonyl, benzyl, para-methoxybenzyl, trityl, tetrahydropyranyl, etc.

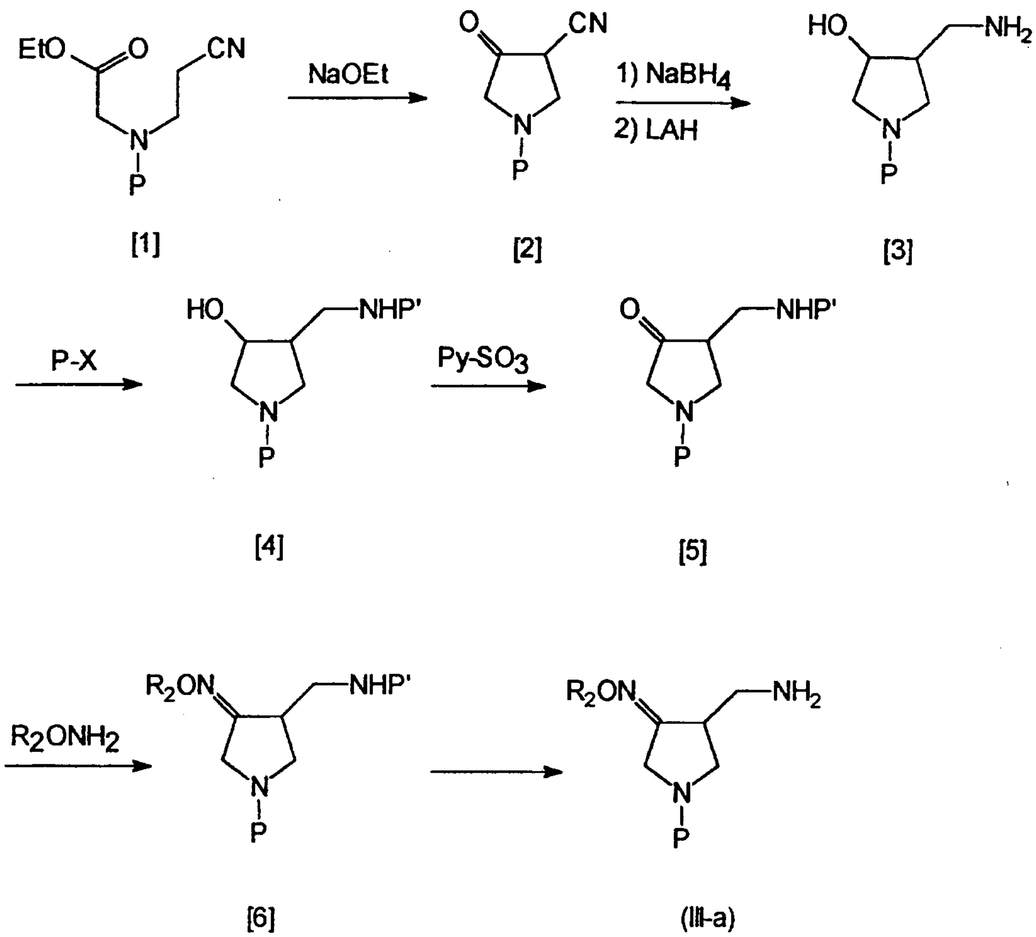
After the reaction is completed, the amino-protecting group present in the resulting compound of formula (I') can be removed by hydrolysis, solvolysis or reduction depending on properties of the relevant protecting group. For example, the compound of formula (I') is treated in a solvent in the presence or absence of an acid or base at the temperature of 0 to 130°C to remove the protecting group. As the acid which can be used for this purpose, an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, etc., an organic acid such as acetic acid, trifluoroacetic acid, formic acid, toluenesulfonic acid, etc., or a Lewis acid such as boron tribromide, aluminum chloride, etc., can be mentioned. As the base for this purpose, hydoxide of an alkali or alkaline earth metal such as sodium hydroxide, barium hydroxide, etc., an alkali metal carbonate such as sodium carbonate, calcium carbonate, etc., an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, etc., or sodium acetate, and the like can be used. The reaction can be carried out in the presence of a solvent, for example, water or an organic solvent such as ethanol, tetrahydrofuran, dioxane, ethyleneglycol, acetic acid, etc., or a mixture of such organic solvent and water. If required, this reaction can also be practiced in the absence of any solvent.

In addition, when the protecting group is para-toluenesulfonyl, benzyl, trityl, para-methoxybenzyl, benzyloxycarbonyl, para-methoxybenzyloxycarbonyl, trichloroethoxycarbonyl, betaiodoethoxycarbonyl and the like, such groups can be effectively removed by means of a reduction. Although the reaction condition of the reduction for removing protecting group may be varied with properties of the relevant protecting group, the reduction can be generally carried out with hydrogen gas stream in an inert solvent in the presence of a catalyst such as platinum, palladium, Raney nickel, etc., at the temperature of 10 to 100°C or with metal sodium or metal lithium in ammonia at the temperature of -50 to -10°C.

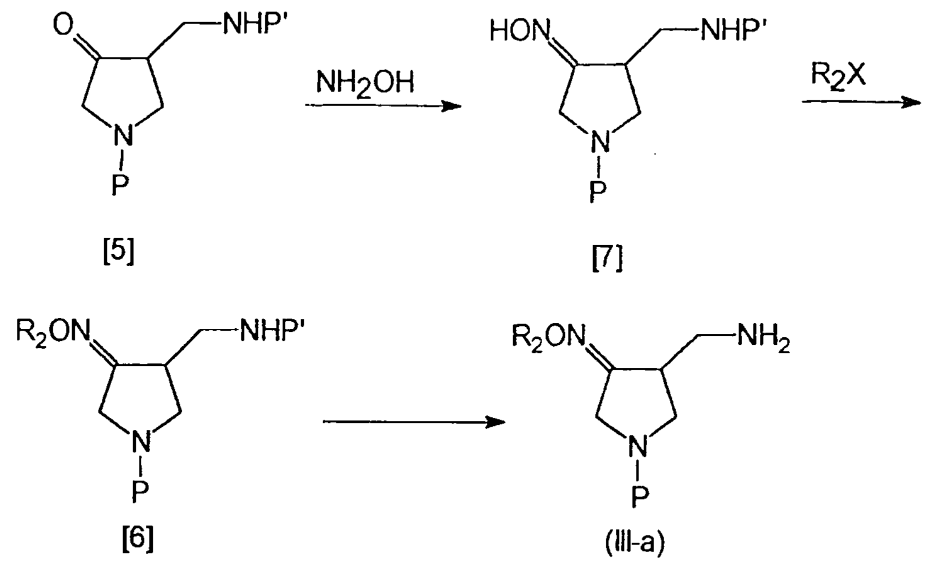
The compound of formula (II) used as the starting material in the present invention is a known compound and can be readily prepared according to a method known in the prior publication (see, J. M. Domagala, et al., J. Med. Chem. 34, 1142 (1991); J. M. Domagala, et al., J. Med. Chem. 31, 991 (1988); D. Bouzard, et al., J. Med. Chem. 35, 518 (1992)).

The compound of formula (III) used as another starting material in the present invention can be readily prepared according to the method as depicted in the following reaction schemes 3, 4 and 5.

Reaction Scheme 3



Reaction Scheme 4



In the above reaction schemes 3 and 4,

the protecting groups P and P' independently of one another represent the same amino-protecting group as defined for P in connection with the compound of formula (III') and can be identical with or different from each other; and

Py represents pyridine.

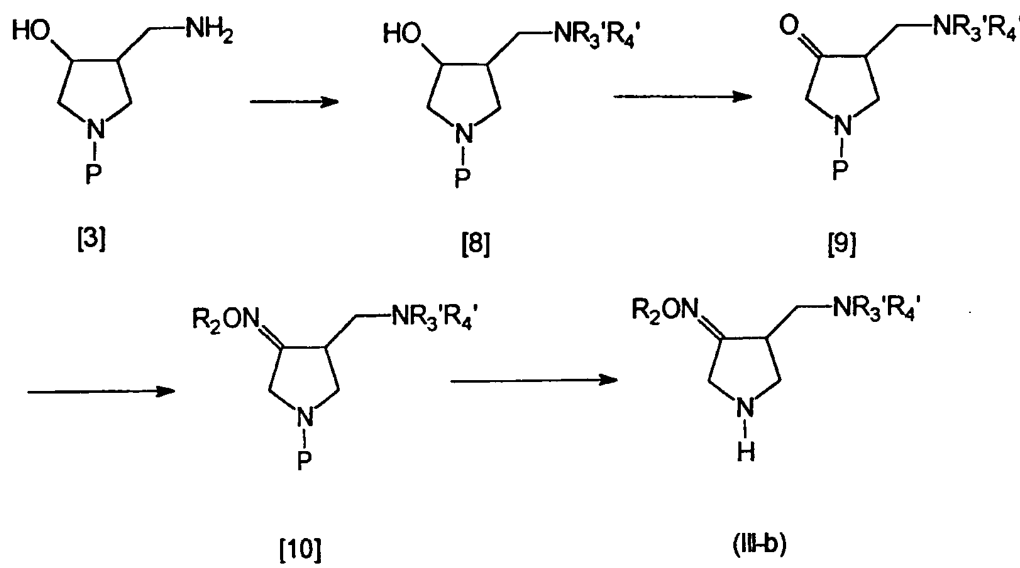
The process depicted in the reaction schemes 3 and 4 will be specifically explained hereinafter.

According to the reaction scheme 3, first a cyano ester [1] having a protected amino group can be reacted with sodium ethoxide in a solvent such as ethanol to obtain a 3-keto-4-cyanopyrrolidine [2]. The resulting cyanopyrrolidine [2] is reduced with hydrogen gas in the presence of a platinum catalyst to prepare an aminoalcohol [3]. In this case, the cyanopyrrolidine [2] may be reduced by means of other reductant to prepare the aminoalcohol [3]. For example, the ketone and cyano groups can be reduced with lithium aluminumhydride(LAH), sodium borohydride-cobalt chloride complex($NaBH_4$-$CoCl_3$) or lithium borohydride($LiBH_4$). Alternatively, the aminoalcohol [3] can be synthesized by reducing first the ketone group to a hydroxyl group by means of sodium borohydride($NaBH_4$) and then reducing the cyano group by lithium aluminum hydride(LAH). Then, the amino group of the aminoalcohol [3] thus prepared is selectively protected to obtain a protected amine [4], which is then treated with sulfur trioxide(SO_3)-pyridine mixture in dimethylsulfoxide solvent (see, Parikh, J.R. and Doering, W. v. E. J. Am. Chem. Soc. 1967, 89, 5505), or oxidized with other oxidant, to prepare a ketone compound [5]. The resulting ketone compound [5] is then reacted with a O-substituted hydroxyamine of formula R_2ONH_2 to obtain the desired substituted oxime compound [6], which can be deprotected by means of a suitable method selected depending on the kind of protecting group to obtain the desired oxime compound (III) wherein R_3 and R_4 are hydrogen, i.e. the compound of formula (III-a).

Alternatively, according to the method depicted in the reaction scheme 4, the ketone compound [5] is reacted with hydroxyamine to obtain the desired oxime compound [7] and the compound [7] is reacted with a suitable electrophilic compound of formula R_2X which can introduce the desired R_2 group, in the presence of a base to prepare the oxime derivative of formula [6], which is then deprotected by means of a suitable method selected depending on the kind of protecting group in the same manner as in the reaction scheme 3 to prepare the desired oxime compound (III-a).

The compound of formula (III) wherein R_3 and R_4 of aminomethyl group present on 4-position of pyrrolidine are other than hydrogen, i.e. the compound of formula (III-b), can be prepared by the following reaction scheme 5.

Reaction Scheme 5



In the above reaction scheme,

R_3' and R_4' represent the same meaning as defined for R_3 and R_4 in connection with the compound of formula (I), provided that they cannot be hydrogen.

According to the method of reaction scheme 5, first the amine compound [3] is treated with C_1-C_3 aldehyde and then reduced to obtain a substituted amine compound [8] and the resulting amine compound [8] is treated with sulfur trioxide(SO_3)-pyridine mixture in dimethylsulfoxide solvent, or oxidized with other oxidant, to obtain a ketone compound [9]. The resulting ketone compound [9] can be treated in the same manner as in the method for treating ketone compound [5] in the reaction schemes 3 and 4 to synthesize the desired compound of formula (III-b).

The synthetic methods as described above will be more specifically explained in the following preparation examples.

The present invention also provides an antibacterial composition comprising the novel compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof as an active component together with a pharmaceutically acceptable carrier. When such antibacterial composition is used for clinical purpose, it may be formulated into solid, semi-solid or liquid pharmaceutical preparations for oral, parenteral or topical administration by combining the compound of formula (I) with a pahrmaceutically acceptable inert carrier. The pharmaceutically acceptable inert carrier which can be used for this purpose may be solid or liquid. The solid or semi-solid pharmaceutical preparation in the form of powders, tablets, dispersible powders, capsules, cachets, suppositories and ointments may be prepared in which case solid carriers are usually used. The solid carrier which can be used is preferably one or more substances selected from the group consisting of diluents, flavouring agents, solubilizing agents, lubricants, suspending agents, binders, swelling agents, etc. or may be encapsulating substances. In the case of powder preparation, the micronized active component is contained in an amount of 5 or 10 to 70% in the carrier. Specific example of the suitable solid carrier includes magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectine, dextrin, starch, gelatin, tragaganth, methylcellulose, sodium carboxymethylcellulose, low boiling wax, cocoa butter, etc. Because of their ease in administration, tablets, powders, cachets and capsules represent the most advantageous solid preparation for oral administration.

The liquid preparation includes solutions, suspensions and emulsions. For example, the injectable preparation for parenteral administration may be in the form of water or water-propyleneglycol solution, of which isotonicity, pH and the like can be adjusted to be suited for the physiological condition of living body. The liquid preparation can also be prepared in the form of a solution in aqueous polyethyleneglycol solution. The aqueous solution for oral administration can be prepared by dissolving the active component in water and adding a suitable coloring agent, flavouring agent, stabilizer and thickening agent thereto. The

aqueous suspension suitable for oral administration can be prepared by dispersing the micronized active component in viscous substances such as natural or synthetic gum, methylcellulose, sodium carboxymethylcellulose and other known suspending agent.

It is especially advantageous to formulate the aforementioned pharmaceutical preparations in dosage unit form for ease of administration and uniformity of dosage. Dosage unit forms of the preparation refer to physically discrete units suitable as unitary dosage, each unit containing a predetermined quantity of the active component calculated to produce the desired therapeutic effect. Such dosage unit form can be in the packaged form, for example, a tablet, a capsule or a powder filled in vial or ampule, or an ointment, gel or cream filled in tube or bottle.

Although the amount of the active component contained in the dosage unit form can be varied, it can be generally adjusted within the range of 1 to 100mg depending on the efficacy of the selected active component.

When the active compound of formula (I) of the present invention is used as a medicine for treatment of bacterial infections, it is preferably administered in an amount of about 6 to 14mg per kg of body weight at the first stage. However, the administration dosage can be varied with the requirement of the subject patient, severity of the infections to be treated, the selected compound and the like.

The preferred dosage suitable for a certain condition can be determined by a person skilled in this art according to a conventional manner. In general, the therapeutic treatment is started from the amount less than the optimal dosage of the active compound and then the administration dosage is increased little by little until the optimal therapeutic effect is obtained. As a matter of convenience, the total daily dosage can be divided into several portions and administered over several times.

As mentioned above, the compound of the present invention shows a potent and broad spectrum antibacterial activity against various pathogenic organisms including gram-positive and gram-negative strains. The antibacterial activity of the present compound against gram-negative strains is comparable to or higher than that of the known antibacterial agents (for example, ciprofloxacin), and particularly, the antibacterial activity of the present compound against gram-positive strains is far superior to that of the known antibacterial agents. In addition, the present compound also exhibits a very potent antibacterial activity against the strains resistant to the known quinolone compounds.

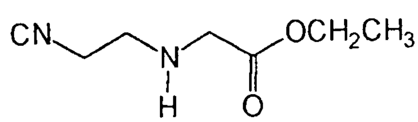
In view of the pharmacokinetic properties, the compound of the present invention has a high water-solubility and thus can be well absorbed in the living body, in comparison with the known quinolone compounds, to show a very high bioavailability. The biological half life of the present compound is far longer than that of the known quinolone compounds, and therefore, the present compound can be administered once a day to be suitably used as an antibacterial agent.

Moreover, since the compound according to the present invention is less toxic, it can be effectively used for prophylaxis and treatment of diseases caused by bacterial infections in warm-blooded animals including human being.

The present invention will be more specifically explained in the following examples. However, it should be understood that the following preparations and examples are intended to illustrate the present invention and not to limit the scope of the present invention in any manner.

Preparation 1

Synthesis of (2-cyano-ethylamino)acetic acid ethyl ester



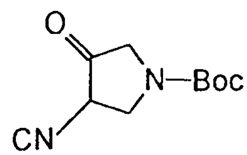
139.6g (1 mole) of glycine ethyl ester hydrochloride was dissolved in 80ml of distilled water and to this solution was added 230ml of an aqueous solution of 67.3g (1.2 mole eq.) of potassium hydroxide. Then, 106.2g (2 mole eq.) of acrylonitrile was added to the reaction solution while heating and stirring at 50 to 60°C. The reaction mixture was stirred for 5 hours with heating and then the organic layer was separated. The aqueous layer was extracted with ethyl ether and the extract was combined with the organic layer as separated above. The combined organic layer was dried over anhydrous magnesium sulfate and filtered.

The filtrate was concentrated under reduced pressure to remove the solvent. The residue was distilled under reduced pressure (100 to 150°C/10.25torr) to obtain 65.6g (Yield: 48%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm) : δ 4.20(2H, q), 3.48(2H, s), 2.96(2H, t), 2.54(2H, t), 1.30(3H, t)
MS (FAB, m/e) : 157(M+H)

Preparation 2

Synthesis of 4-cyano-1-(N-t-butoxycarbonyl)-pyrrolidin-3-one

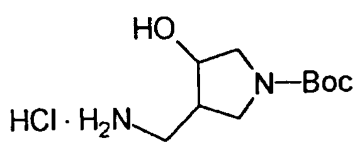


In the above formula and the following, Boc represents t-butoxycarbonyl. 29g (0.186 mole) of the compound prepared in Preparation 1 was dissolved in 200ml of chloroform and the resulting solution was introduced into a 1 L flask. Then, 45g (1.1 mole eq.) of di-t-butoxycarbonyldicarbonate was added thereto and the reaction mixture was stirred for 17 hours at room temperature. The reaction solution was concentrated and the residue was diluted with 250ml of absolute ethanol. The resulting solution was added to sodium ethoxide (NaOEt) solution prepared by adding 6g of metal sodium (Na) turnings to 220ml of absolute ethanol, under refluxing and heating. The reaction was continuously conducted for further one hour under refluxing with heating. The reaction solution was concentrated under reduced pressure and the residue was diluted with water and then washed with methylene chloride. The aqueous layer was adjusted with 1N HCl to pH 4 and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated to obtain a stoichiometric amount of the title compound in a crude state.

^{1}H NMR ($CDCl_3$, ppm) : δ 4.5-3.5(5H, m), 1.5(9H, s)
MS (FAB, m/e) : 211(M+H)

Preparation 3

Synthesis of 4-aminomethyl-1-(N-t-butoxycarbonyl)pyrrolidin-3-ol hydrochloride

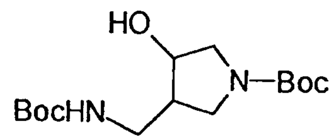


3g (14 mmole) of the compound prepared in Preparation 2 was dissolved in the mixture of 357ml of absolute ethanol and 7ml of chloroform and the resulting solution was introduced into a flask. Then, a catalytic amount of platinum oxide(PtO_2) was added thereto. After air was removed from the reaction flask under reduced pressure, the reaction mixture was stirred for 17 hours at room temperature with blowing up the hydrogen gas from a balloon filled with hydrogen gas. The reaction solution was filtered and the filtrate was concentrated to obtain a stoichiometric amount of the title compound.

^{1}H NMR ($CDCl_3$, ppm) : δ 8.0(2H, bs), 3.5-2.0(7H, m), 3.3(2H, s), 1.38(9H, s)
MS (FAB, m/e) : 217(M+H)

Preparation 4

Synthesis of 4-(N-t-butoxycarbonyl)aminomethyl-1-(N-t-butoxycarbonyl)pyrrolidin-3-ol



Method A :

20g (0.094 mole) of the compound prepared in Preparation 3 was dissolved in the mixture of 456ml of dioxane and 268ml of distilled water and the resulting solution was adjusted with 1N aqueous sodium hydroxide solution to pH 9. Then, 30.9g (1.5 mole eq.) of di-t-butoxycarbonyldicarbonate was added thereto, and the reaction mixture was stirred for 30 minutes at room temperature and concentrated under reduced pressure. The residue was diluted with methylene chloride. After adding water to the reaction solution, the organic layer was separated and the aqueous layer was acidified to pH 4 and then extracted with methylene chloride. The extract was combined with the organic layer as separated above and the combined solution was dried over anhydrous magnesium sulfate and concentrated. The residue was purified with column chromatography to obtain 17g (Yield: 57%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm) :	δ 4.95(1H, m), 4.1(1H, m), 3.5(2H, m), 3.3-3.0(4H, m), 2.1(1H, m), 1.45(18H, s)
MS (FAB, m/e) :	317(M + H)

Method B :

10g (0.047 mole) of the compound prepared in Preparation 2 was introduced into a 1 L flask and then dissolved by adding 500ml of dry tetrahydrofuran. This solution was cooled to -3°Cunder ice-sodium chloride bath and then 3.8g (0.094 mole) of lithium aluminumhydride(LAH) was added portionwise thereto over 20 minutes. After the addition is completed, the reaction mixture was stirred for one hour under ice-water bath. When the reaction is completed, 4ml of water, 4ml of 15% aqueous sodium hydroxide solution and 12ml of water were carefully and successively added to the reaction mixture. The whole mixture was vigorously stirred for 3 hours at room temperature and 10g of anhydrous magnesium sulfate was added thereto. This mixture was stirred and then filtered, and the filtrate was concentrated to stoichiometrically obtain the product. The resulting product was diluted with 200ml of dioxane-water (2:1 by volume) and 12.3g (0.056 mole) of di-t-butoxycarbonyldicarbonate was added thereto at room temperature. The reaction solution was stirred for one hour at room temperature to complete the reaction and then concentrated. The residue was diluted again with ethyl acetate, washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated and the residue was then purified with column chromatography using hexane-ethyl acetate (2:1 by volume) eluant to obtain 8.2g (Yield: 55%) of the title compound.

Method C :

210g (1 mole) of the compound prepared in Preparation 2 was dissolved in 4 L of methanol and this solution was introduced into a 6 L reaction vessel equipped with a thermometer. The internal temperature of the reaction vessel was cooled to 10°Cunder dry ice-acetone bath. 76g (2 mole) of sodium borohydride ($NaBH_4$) was added portionwise thereto over 1.5 hours while maintaining the internal temperature of the vessel at 10 to 13°C. After the addition is completed, the reaction mixture was stirred for further 30 minutes at the same temperature so that all the ketone can be reduced to alcohol. Then, 243g (1 mole) of cobalt chloride hydrate was added thereto over 10 minutes. When the reaction is completed, the resulting solid complex was dissolved in 4 L of ammonia water and this solution was diluted with 8 L of water and then extracted with ethyl acetate. The organic layer was washed with saturated saline, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated and mixed with the mixture of 1.5 L of dioxane and 0.5 L of distilled water. 212g of di-t-butoxycarbonyldicarbonate was added thereto and the whole

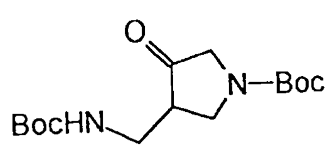
mixture was stirred for 2 hours at room temperature. After the reaction is completed, the reaction mixture was concentrated under reduced pressure, diluted again with dichloromethane, washed with water, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated and then purified with silica gel column chromatography (eluant: hexaneethyl acetate 2:1 by volume) to obtain 202g (Yield: 64%) of the title compound.

Method D :

10g (0.047 mole) of the compound prepared in Preparation 2 was introduced into a 1 L flask and dissolved by adding 500ml of methanol. This solution was cooled down under ice bath and 3.6g (0.094 mole) of sodium borohydride was added portionwise thereto over 20 minutes. The reaction mixture was stirred for further 30 minutes to complete the reaction, and then concentrated under reduced pressure, diluted with ethyl acetate, washed with water, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated to obtain the compound in which the desired ketone group is reduced to an alcohol. 10.1g (0.047 mole) of the resulting alcohol compound was dissolved in 200ml of dry tetrahydrofuran and this solution was cooled down to -5°Cunder ice-salt bath. 2.6g (0.066 mole) of lithium aluminumhydride was added thereto over 20 minutes. The reaction mixture was stirred for further 30 minutes at the same temperature to complete the reaction, and then 2.6ml of water, 2.6ml of 15% sodium hydroxide and 7.8ml of water were added in order thereto. This mixture was stirred for one hour at room temperature. After adding 6g of anhydrous magnesium sulfate, the mixture was stirred for further 30 minutes and filtered. The filtrate was concentrated to obtain the product. The resulting product was diluted with 200ml of dioxane-water (2:1 by volume) and 12.3g (0.056 mole) of di-t-butoxycarbonyldicarbonate was added portion-wise thereto. The mixture was stirred for 30 minutes to complete the reaction, and then concentrated, diluted with ethyl acetate, washed with saturated saline, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated and the residue was purified with column chromatography to obtain 12.3g (Yield: 83%) of the title compound.

Preparation 5

Synthesis of 4-(N-t-butoxycarbonyl)aminomethyl-1-(N-t-butoxycarbonyl)pyrrolidin-3-one

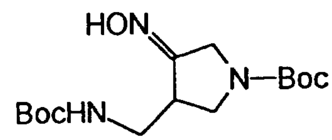


14g (0.044 mole) of the compound prepared in Preparation 4 was dissolved in 64ml of dimethylsulfoxide and 18.5ml (3 mole eq.) of triethylamine was added thereto. This mixture was cooled down under ice bath. When the wall of reaction flask begins to freeze, 12.7g (1.8 mole eq.) of pyridine-sulfur trioxide(Py-SO_3) oxidant was added portionwise thereto. After the addition is completed, the ice bath was removed and the reaction solution was stirred for 3 hours at room temperature, diluted with water and then extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and concentrated to stoichiometrically obtain the title compound in a crude state.

^{1}H NMR ($CDCl_3$, ppm) : δ 4.95(1H, bs), 4.15-2.7(6H, m), 2.8 (1H, br), 1.45(9H, s), 1.40(9H, s)
MS (FAB, m/e) : 315 (M+H)

Preparation 6

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)aminomethyl-pyrrolidin-3-one oxime



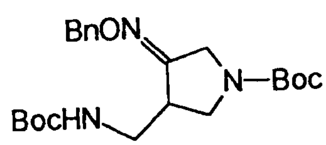
300mg of the compound prepared in Preparation 5 was dissolved in the mixture of 6ml of 95% ethanol and 3ml of tetrahydrofuran(THF) and this solution was introduced into a 30ml reaction vessel. 232mg (3.5 mole eq.) of hydroxyamine hydrochloride ($NH_2OH \cdot HCl$) was added thereto and then 281mg (3.5 mole eq.) of sodium hydrogen carbonate dissolved in 1.5ml of distilled water was added. The reaction mixture was stirred for 40 minutes at 40°C under oil bath to complete the reaction, cooled down and then concentrated under reduced pressure. The residue was diluted with methylene chloride, washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated and the residue was subjected to silica gel column chromatography eluting with hexane-ethyl acetate (1:1 by volume) to obtain 230mg (Yield: 73%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm) : δ 9.70(1H, bs), 5.05(1, bs), 4.2(2H, br), 3.83(1H, m), 3.5-3.2(3H,m), 3.0(1H, m), 1.42(18H, s)

Ms (FAB, m/e) : 330(M+H)

Preparation 7

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)aminomethyl-pyrrolidin-3-one-benzyloxime



659mg of the compound prepared in Preparation 6, 193mg of tetra-n-butylammonium bromide and 855mg of benzyl bromide were added to 15ml of dichloromethane and then 5ml of 15% aqueous sodium hydroxide solution was added thereto. The reaction mixture was stirred for 30 minutes at room temperature. The organic layer was separated, dried over anhydrous magnesium sulfate and filtered. The filtrate was distilled under reduced pressure and the residue was purified with glass column chromatography to obtain 776mg (Yield: 92%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm) : δ 7.38(5H, m), 5.13(2H, s), 4.92(1H, m), 4.13(2H, m), 3.76(1H, m), 3.41(1H, m), 3.25(2H m), 3.02(1H, m), 1.50(9H, s), 1.49(9H, s)

MS (FAB, m/e) : 420(M+H)

Preparations 8 to 17

The amine compounds listed in the following Table 1 were prepared according to the same procedure as Preparation 7 except that the corresponding benzylbromide derivatives having R_2 structure as presented in the following Table 1 are used instead of benzylbromide.

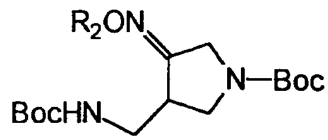
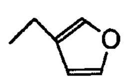
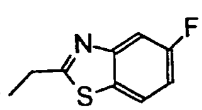
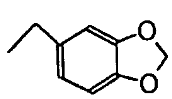
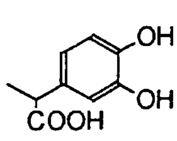
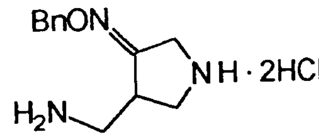


Table 1. Preparations 8 to 17

Prep.	R_2	NMR($CDCl_3$), δ(ppm)	FAB MS(M+H)
8	4-nitrobenzyl	8.2(2H,m), 7.4(2H,m), 5.2(2H,s), 4.9(1H, s), 4.2(2H,m), 3.8(1H,m), 3.5-3.2(3H,m), 3.0(1H,m), 1.5(18H,s)	465
9	4-methoxybenzyl	7.3(2H,m), 6.9(2H,m), 5.0(2H,s), 4.9(1H, s), 4.1(2H,m), 3.8(3H,s), 3.75(1H,m), 3.5-3.0(4H,m), 1.45(18H,s)	450
10	4-fluorobenzyl	7.3(2H,m), 7.0(2H,m), 5.0(2H,s), 4.8(1H, br), 4.2(2H,m), 3.9(1H,m), 3.4(3H,m), 3.0(1H,m), 1.46(18H,s)	438
11	4-t-butylbenzyl	7.4-7.3(4H,m), 5.1(2H,s), 5.0(1H,s), 4.1(2H,m), 3.8(1H,m), 3.6-3.0(4H,m), 1.45(18H,s), 1.3(9H,s)	476
12	2-cyanobenzyl	7.8-7.3(4H,m), 5.3(2H,s), 5.0(1H,bs), 4.2(2H,s), 3.9(1H,m), 3.6-3.2(3H,m), 3.0(1H,s), 1.5(18H,s)	445
13	3-pyridylmethyl	8.6(2H,m), 7.7(1H,m), 7.3(1H,m), 5.1(2H, s), 4.9(1H,s), 4.1(2H,m), 3.8(1H,m), 3.6-3.2(3H,m), 3.0(1H,m), 1.5(18H,s)	421
14		7.4(2H,m), 6.5(1H,m), 4.9(2H,s), 4.9(1H,s), 4.1(2H,m), 3.8(2H,m), 3.2(3H,m), 1.5(18H,s)	410
15		7.7(2H,m), 7.2(1H,m), 5.5(1H,s), 5.0(1H,s), 4.2(2H,m), 3.8(1H,m), 3.6-3.1(4H,m), 1.5(18H,s)	495
16		6.9(3H,m), 6.0(2H,m), 5.0(3H,m), 4.1(2H,m), 3.8(1H,m), 3.6-3.2(3H,m), 3.0(1H,m), 1.5(18H,s)	464
17		7.3-7.0(3H,m), 6.8(1H,s), 5.1(1H,s), 4.2(2H,m), 3.8(1H,m), 3.5-3.0(4H,m), 1.6-1.4(27H,s)	496

Preparation 18

Synthesis of 4-aminomethyl-pyrrolidin-3-one-benzyloxime dihydrochloride



20ml of methanol was cooled down to 5°C and then 10ml of acetyl chloride was slowly added thereto. This mixture was stirred for 30 minutes and 990mg of the compound prepared in Preparation 7, which is dissolved in 10ml of methanol, was added thereto. The reaction mixture was stirred for 50 minutes at room temperature and concentrated under reduced pressure. The residue was washed with ethyl acetate and dried to obtain 648mg (Yield: 94%) of the title compound as a yellow solid.

^{1}H NMR (DMSO-d_6, ppm) : δ 10.0(1H, m), 8.35(2H, m), 7.40(5H, m), 5.18(2H, s), 4.00(2H, m), 3.69-(1H, m), 3.40(2H, m), 3.12(2H, s)

MS (FAB, m/e) : 220(M + H)

Preparations 19 to 28

The compounds listed in the following Table 2 were prepared from the amine compounds prepared in Preparations 8 to 17 according to the same procedure as Preparation 18.

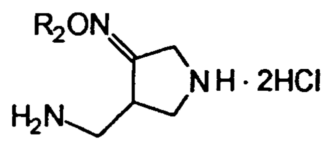
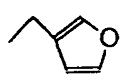
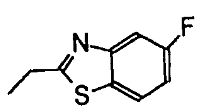
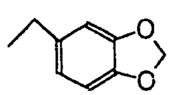
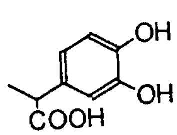
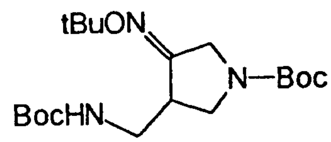


Table 2. Preparations 19 to 28

Prep.	R_2	NMR($CDCl_3$), δ(ppm)	FAB MS(M+H)
19	4-nitrobenzyl	10.3-10.1(2H,s), 8.3(3H,s), 8.2(2H,d), 7.7(2H,d), 5.3(2H,s), 4.1(2H,m), 3.7(1H, m), 3.4(2H,m), 3.1(2H,m)	265
20	4-methoxybenzyl	10.2-10.0(2H,s), 8.4(3H,s), 7.3(2H,d), 6.9(2H,d), 5.0(2H,s), 3.9(2H,m), 3.73(3H, s), 3.7(1H,m), 3.4(2H,m), 3.1(2H,m)	250
21	4-fluorobenzyl	10.2(2H,s), 8.4(3H,s), 7.3(2H,m), 7.2(2H, m), 5.1(2H,s), 3.9(2H,m), 3.7(1H,m), 3.4(2H,m), 3.1(2H,m)	238
22	4-t-butylbenzyl	10.2(2H,s), 8.4(3H,s), 7.4-7.3(4H,m), 5.1(2H,s), 3.9(2H,m), 3.7(1H,m), 3.2 (2H,m), 3.1(2H, m), 1.3(9H,s)	276
23	2-cyanobenzyl	10.2-10.0(2H,s), 8.2(3H,s), 7.9-7.5(4H, m), 5.3(2H,s), 4.0(2H,m), 3.7(1H,m), 3.2(2H,m), 3.1(2H,m)	245
24	3-pyridylmethyl	10.3(1H,s), 10.1(1H,s), 8.9(1H,s), 8.8 (1H,m), 8.5(1H,d), 8.4(3H,m), 8.0(1H,m), 5.4(2H,s), 4.0(2H,m), 3.7(1H,m), 3.4 (2H,m), 3.1(2H,m)	221
25		10.3(2H,s), 8.4(3H,s), 7.6(1H,s), 6.4(1H,s), 5.0(2H,s), 4.0(2H,m), 3.8(1H,m), 3.4(2H,m), 3.1(2H,m)	210
26		10.3(2H,s), 8.3(3H,s), 8.1(1H,m), 7.9 (1H,m), 7.4(1H,m), 5.5(2H,s), 4.1(2H,m), 3.9(1H,m), 3.14(2H,m), 3.1(2H,m)	295
27		10.2(2H,s), 8.3(3H,s), 7.0(3H,m), 6.3 (2H,s), 5.3(2H,m), 4.1(2H,m), 3.9(1H,m), 3.4-3.2(2H,m), 3.1(2H,m)	264
28		10.3-10.2(2H,s), 8.4(3H,s), 8.0-7.3(3H, m), 7.0(1H,s), 4.2(2H,m), 3.8(1H,m), 3.5-3.2(3H,m), 3.0(1H,m)	296

Preparation 29

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)aminomethyl-pyrrolidin-3-one t-butyloxime



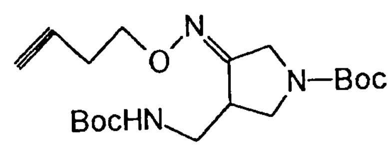
300mg of the compound prepared in Preparation 5 was dissolved in the mixture of 6ml of 95% ethanol and 3ml of tetrahydrofuran(THF) and this solution was introduced into a 30ml reaction vessel. 487mg (3.5 mole eq.) of o-t-butylhydroxyamine hydrochloride was added thereto and then 281mg (3.5 mole eq.) of sodium hydrogen carbonate dissolved in 1.5ml of distilled water was added. The reaction mixture was stirred for 40 minutes at 40°C under oil bath to complete the reaction, and then cooled down, concentrated under reduced pressure, diluted with methylene chloride, washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated and the residue was subjected to silica gel column chromatography eluting with hexane-ethyl acetate (1:1 by volume) to obtain 285mg (Yield: 80%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm) : δ 5.10(1H, bs), 4.05(2H, s), 3.71(1H, dd), 3.43(1H, br), 3.2(2H, m), 3.0(1H, m), 1.42(18H, s), 1.30(9H, s)

MS (FAB, m/e) : 386(M+H)

Preparation 30

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)aminomethyl-pyrrolidin-3-one 3-butynyloxime



A. Synthesis of 3-butynyl hydroxylamine

0.35g (5 mmole) of 3-butynol, 0.86g (5.25 mmole) of N-hydroxyphthalimide and 1.44g (5.5 mmole) of triphenylphosphine were dissolved in 15ml of dry tetrahydrofuran, and then 1.05g (6 mmole) of diethylazodicarboxylate was added thereto over 30 minutes. The mixture was stirred for 10 minutes at room temperature and then distilled under reduced pressure to remove the solvent. To the residue was added 50ml of ethyl acetate-hexane (1:1 v/v). The precipitated solid material was filtered off and the filtrate was concentrated. The residue was purified with column chromatography (hexane-ethyl acetate 9:1 v/v). The resulting white solid [0.54g, Yield 50%, ^{1}H NMR ($CDCl_3$, ppm) : δ 7.85(2H, m), 7.75(2H, m), 4.2(2H, t), 2.8-(2H, dd), 2.5(2H, dd), 2.1(1H, s), FAB MS(POS) : $[M+H]^+$ = 216] was dissolved in 12ml of methylene chloride, and 0.25g (5 mmole) of hydrazine hydrate diluted with 4ml of methanol was added dropwise thereto. The solid precipitate was filtered off and the filtrate was concentrated at low temperature under reduced pressure to obtain 0.2g (Yield: 93%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm) : δ 9.5(2H, br), 4,5(2H, t), 2.8(2H, m), 2.4(2H, m), 2.05(1H, s)

MS (FAB, m/e) : $86(M+H)^+$

B. Synthesis of the title compound

0.45g (1.43 mmole) of the compound prepared in Preparation 5 and 0.2g (2.35 mmole) of 3-butynyl hydroxyamine were dissolved in 5 ml of methanol and the reaction was conducted for 12 hours at 60°C. The reaction solution was concentrated under reduced pressure and the residue was subjected to column

chromatography (ethyl acetate-hexane 1:4 v/v) to obtain 0.59g (stoichiometric amount) of the title compound.

^1H NMR ($CDCl_3$, ppm) : δ 5.0(1H, m), 4.15(2H, t), 4.0(2H, s), 3.75(1H, m), 3.6-3.2(3H, m), 3.0(1H, m), 2.5(2H, m), 2.0(1H, s), 1.45(18H, s)

FAB MS (POS) : $382(M+H)^+$

Preparations 31 to 36

The amine compounds listed in the following Table 3 were prepared according to the same procedure as Preparation 30 except that the corresponding alcohol derivatives having R_2 structure as represented in the following Table 3 are used instead of 3-butynol.

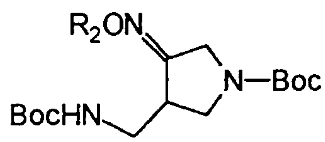
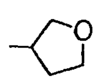
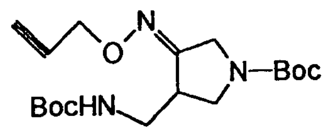


Table 3. Preparations 31 to 36

Prep.	R_2	^1H NMR($CDCl_3$), δ(ppm)	FAB MS(M+H)
31	isopropyl	5.0(1H,br), 4.1(2H,s), 4.0(1H,m), 3.4 (1H,m), 3.55-3.25(3H,m), 3.0(1H,m), 1.55(18H,s), 1.0(6H,d)	372
32	cyclobutyl	4.7(1H,m), 4.2(2H,s), 3.8(1H,m), 3.4(1H, m), 3.3(2H,m), 3.0(1H,m), 2.3(2H,m), 2.1 (2H,m), 1.8(1H,m), 1.6(1H,m), 1.5(18H,s)	384
33	cyclopentyl	4.7(1H,m), 4.1(2H,m), 3.7(1H,m), 3.4(1H,m), 3.3(2H,m), 3.0(1H,m), 1.8(4H,m), 1.7(4H,m), 1.6(18H,s)	398
34		5.0-4.8(1H,m), 4.3-3.7(6H,m), 3.3(2H,m), 3.0(1H,m), 2.1(2H,m), 1.5(18H,s), 1.3(2H,m)	400
35	cyclopropyl-methyl	5.1(1H,br), 4.1(2H,m), 3.9(2H,m), 3.8(1H, m), 3.5(1H,m), 3.3(2H,m), 3.0(1H,m), 1.5 (18H,s), 1.1(1H,m), 0.6(2H,s), 0.3(2H,s)	384
36	isobutyl	5.05(1H,br), 4.15(2H,s), 4.1(2H,d), 3.6(2H,m), 3.3(1H,m), 3.0(2H,m), 2.5(1H,m), 1.5(18H,s), 1.05(6H,d)	386

Preparation 37

Synthesis of 1-(N-t-butoxycarbonyl)-4-(N-t-butoxycarbonyl)aminomethyl-pyrrolidin-3-one propargyl oxime



659mg of the compound prepared in Preparation 6, 193mg of tetra-n-butylammonium bromide and 855mg of propargyl bromide were added to 15ml of dichloromethane, and 5ml of 15% aqueous sodium hydroxide solution was added thereto. This mixture was stirred for 30 minutes at room temperature. The organic layer was separated, dried over anhydrous magnesium sulfate and then filtered. The filtrate was distilled under reduced pressure and the residue was purified with glass column chromatography to obtain 776mg (Yield: 92%) of the title compound.

^{1}H NMR ($CDCl_3$, ppm) : δ 4.92(1H, m), 4.13(2H, m), 3.76(1H, m), 3.41(1H, m), 3.25(2H, m), 3.02(1H, m), 1.50(9H, s), 1.49(9H, s)

MS (FAB, m/e) : 368(M + H)

Preparations 38 and 39

The amine compounds listed in the following Table 4 were prepared according to the same procedure as Preparation 37 except that the corresponding alkyl derivatives having R_2 structure as represented in the following Table 4 are used instead of propargyl.

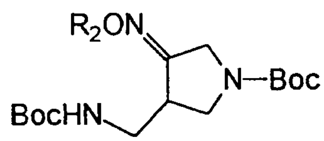
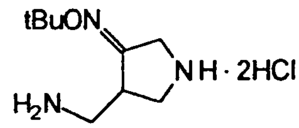


Table 4

Preparations 38 and 39			
Prep.	R_2	^{1}H NMR($CDCl_3$), δ(ppm)	FAB MS(M + H)
38	methoxymethyl	5.15-4.9(3H), 4.15(2H,m), 3.75(1H,m), 3.5-3.2(5H), 3.0(1H,m), 1.5(18H,s)	374
39	2-chloroethyl	4.9(1H,m), 4.3(2H,t), 4.1(2H,s), 3.7(3H,m), 3.6(1H,m), 3.5-3.0(3H,m), 1.45(18H,s)	392

Preparation 40

Synthesis of 4-aminomethyl-pyrrolidin-3-one t-butyloxime dihydrochloride



5ml of methanol was cooled down to 0°C and 3ml of acetyl chloride was slowly added thereto. This mixture was stirred for 10 minutes and 640mg of the compound prepared in Preparation 29, which is dissolved in 10ml of methanol, was added thereto. The reaction mixture was stirred for 20 minutes at room temperature and concentrated under reduced pressure. The residue was filtered, washed with ethylether and dried to obtain 390mg (Yield: 91%) of the title compound as a white solid.

^{1}H NMR (DMSO-d_6, ppm) : δ 10.0-9.6(2H, bsX2), 8.20(3H, br), 3.90(2H,dd), 3.61(1H, bs), 3.40(2H, bs), 3.12(2H, bs), 1.25(9H, s)

MS (FAB, m/e) : 186(M+H)

Preparations 41 to 50

The compounds of Preparations 41 to 50 as listed in the following Table 5 were prepared from the compounds prepared in Preparations 30 to 40 according to the same procedure as Preparation 40.

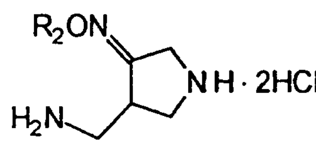
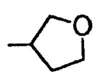
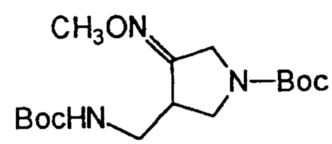


Table 5. Preparations 41 to 50

Prep.	R_2	^1H NMR($CDCl_3$), δ(ppm)	FAB MS(M+H)
41	$CH_2CH_2C{\equiv}CH$	10.1-9.8(2H,br), 8.2(3H,br), 4.3(2H,t), 4.0(2H,s), 3.7(1H,m), 3.6-3.2(3H,m), 3.0(1H,m), 2.8(1H,s), 2.6(2H,t)	182
42	isopropyl	10.1-9.8(2H,br), 8.3(3H,br), 4.4(1H,m), 3.9(2H,d), 3.7(1H,m), 3.3(2H,s), 3.1(2H,m), 1.2(6H,d)	172
43	cyclobutyl	10.2-9.8(2H,br), 8.2(3H,br), 4.8(1H,m), 4.3(2H,s), 3.7(1H,m), 3.6-3.2(3H,m), 3.0(1H,m), 1.8(2H,m), 1.7(2H,m), 1.5(1H,m), 1.45(1H,m)	184
44	cyclopentyl	10.2-9.8(2H,br), 8.2(3H,br), 4.7(1H,m), 4.3(2H,s), 3.8(1H,m), 3.3(1H,m), 3.2(3H, m), 1.8(4H,m), 1.6(2H,m), 1.5(2H,m)	198
45		10.1-9.8(2H,br), 8.3(3H,s), 4.1-3.6 (10H,m), 3.2(2H,s), 2.2-1.9(2H,m)	200
46	cyclopropyl-methyl	10.1-9.8(2H,br), 8.3(3H,s), 4.0-3.8 (4H,m), 3.65(1H,m), 3.4(2H,m), 3.1(2H,m), 1.1(1H,m), 0.5(2H,d), 0.2(2H,d)	184
47	isobutyl	10.3-9.9(2H,br), 8.4(3H,br), 3.9-3.8 (4H,m), 3.65(1H,m), 3.3(2H,s), 3.1(2H,m), 1.9(1H,m), 0.85(6H,d)	186
48	propargyl	10.0(1H,m), 8.3(2H,m), 4.8(2H,s), 4.0(2H,m), 3.7(1H,m), 3.6(1H,s) 3.4(2H,m), 3.1(2H,s)	168
49	methoxymethyl	10-9.6(2H,br), 8.2(3H,br), 5.1(2H,dd) 4.1-3.8(2H,m), 3.7(1H,m), 3.3-3.0(4H,m)	174
50	2-chloroethyl	10-9.7(2H,br), 8.2(3H,br), 4.3(2H,t), 4.0(2H,m), 3.8(2H,t), 3.7(1H,m), 3.4(2H,m), 3.2(1H,m), 3.1(2H,m)	192

Preparation 51

Synthesis of 4-(N-t-butoxycarbonyl)aminomethyl-1-(N-t-butoxycarbonyl)pyrrolidin-3-one O-methyloxime



260mg (8.28×10^{-4} mole) of the compound prepared in Preparation 5 was dissolved in the mixture of 5ml of 95% ethanol and 2.5ml of tetrahydrofuran and this solution was introduced into a reaction vessel. Then, 256mg (3.7 mole eq.) of methoxyamine hydrochloride was added thereto and 257mg (3.7 mole eq.) of sodium hydrogen carbonate($NaHCO_3$) dissolved in 2.5ml of distilled water was also added. The reaction mixture was stirred for 1 hours at 40°C under oil bath, concentrated under reduced pressure, washed successively with aqueous ammonium chloride solution and aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and then filtered. The filtrate was concentrated to obtain 250mg (Yield: 88%) of the title compound.

^1H NMR ($CDCl_3$, ppm) : δ 4.98(1H, bs), 3.81(3H, s), 3.75-2.80(7H, m), 1.40(18H, s)
MS (FAB, m/e) : 344(M+H)

Preparations 52 and 53

The compounds listed in the following Table 6 were prepared according to the same procedure as Preparation 51 except that phenoxyamine hydrochloride or ethoxyamine hydrochloride are used instead of methoxyamine hydrochloride.

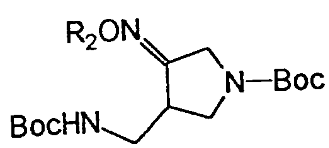
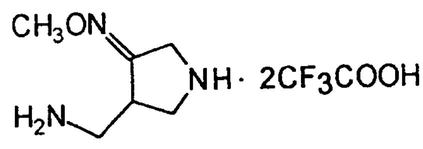


Table 6

Preparations 52 and 53			
Prep.	R_2	^1H NMR($CDCl_3$), δ(ppm)	FAB MS(M+H)
52	phenyl	7.3(5H,m), 4.97(1H,bs), 3.8-2.8(7H,m), 1.40(18H,s)	406
53	$-CH_2CH_3$	5.0(1H,bs), 3.8-2.8(7H,m), 1.42(18H,s), 1.41(18H,s), 1.38(3H,t)	358

Preparation 54

Synthesis of 4-aminomethyl-pyrrolidin-3-one O-methyloxime ditrifluoroacetate



5ml of trifluoroacetic acid was added to 250mg of the compound prepared in Preparation 51, and this mixture was stirred for 20 minutes at room temperature. The reaction mixture was concentrated under reduced pressure, dissolved in the smallest amount of acetonitrile and then solidified with ethylether to obtain 220mg (Yield: 84%) of the title compound in a purified state.

^{1}H NMR (CD_3OD, ppm) : δ 4.1(2H, s), 3.96(3H, s), 3.83(1H, dd), 3.7-3.2(6H, m)
MS (FAB, m/e) : 144(M+H)

Preparations 55 to 57

The corresponding compounds of Preparations 55 to 57 were prepared from the compounds prepared in Preparations 6, 52 and 53, respectively, according to the same procedure as Preparation 54.

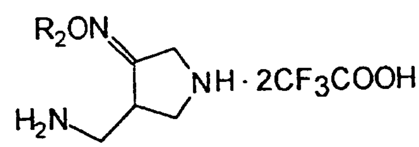
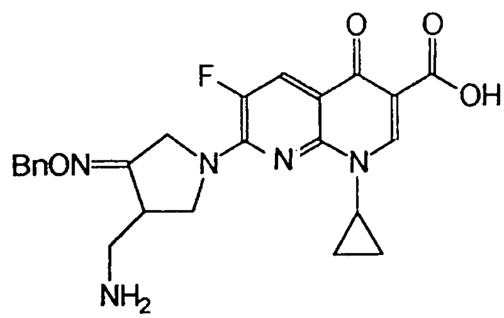


Table 7

Preparations 55 to 57			
Prep.	R_2	^{1}H NMR($CDCl_3$), δ(ppm)	FAB MS(M+H)
55	-H	4.1-3.2(7H, m)	130
56	-Ph	7.2-7.4(5H, m), 4.1-3.2(7H, m)	206
57	$-CH_2CH_3$	4.2-3.1(9H, m), 1.3(3H, t)	158

Example 1

Synthesis of 7-(4-aminomethyl-3-benzyloxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid



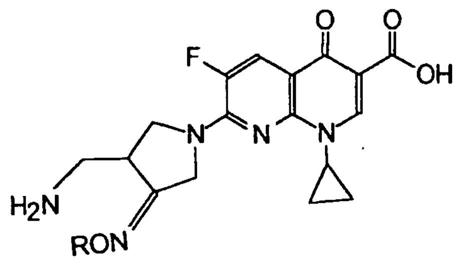
622mg of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid and 643mg of the compound prepared in Preparation 18 were suspended in 15ml of acetonitrile. This suspension was cooled down under ice-water bath and then 1.0ml of 1,8-diazabicyclo[5.4.0]undec-7-ene-(DBU) was slowly added thereto. The reaction mixture was stirred for 1.5 hours at room temperature and, after adding 15ml of water, was then concentrated. The concentrated suspension was filtered. The filtered solid product was washed with water and ethanol to obtain 584mg (Yield: 57%) of the title compound.

^1H NMR (DMSO-d_6, ppm) :	δ 8.59(1H, s), 8.03(1H, d), 7.40(5H, m), 5.14(2H, s), 4.75(2H, s), 4.18(1H, m), 3.94(1H, m), 3.83(1H, m), 3.35(2H, m), 3.05(1H, m), 2.81(1H, m), 2.73-(1H, m), 1.25-1.05(4H, m)
MS (FAB, m/e) :	466(M+H)

Examples 2 to 11

The same starting material as Example 1 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 1 to prepare the respective compounds listed in the following Table 8.

Table 8. Examples 2 to 11



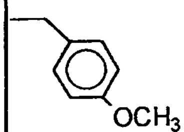
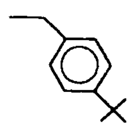
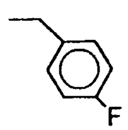
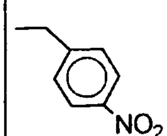
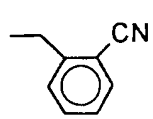
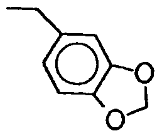
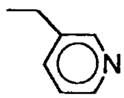
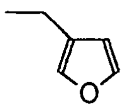
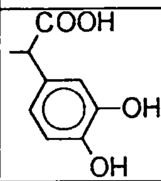
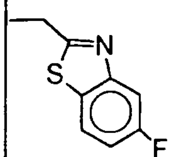
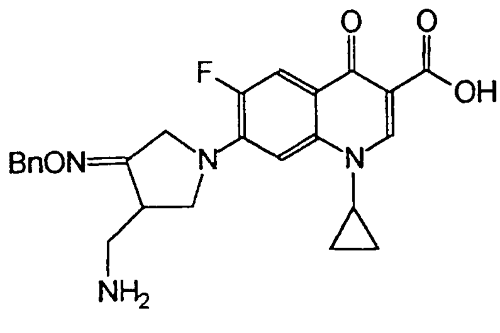
Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (min)	Yield (%)
2		8.73(1H,s),8.05(1H,d),7.30(2H,d),6.98(2H,d),5.10(2H,s),4.61(2H,s),4.25(1H,m),3.90(1H,m),3.80(3H,s),3.70(1H,m),3.00(3H,m),1.26(2H,m),1.07(2H,m)	$CDCl_3$	496	10	75
3		8.75(1H,s),8.05(1H,d),7.45(2H,d),7.30(2H,d),5.15(2H,s),4.62(2H,s),4.25(1H,m),3.85(1H,m),3.75(1H,m),3.10(1H,m),2.98(2H,m),1.35(9H,s),1.25(2H,m),1.09(2H,m)	$CDCl_3$	522	15	76
4		8.68(1H,s),8.00(1H,d),7.35(2H,m),7.10(2H,m),5.08(2H,s),4.59(2H,s),4.20(1H,m),3.95(1H,m),3.81(1H,m),3.00(3H,m),1.23(2H,m),1.04(2H,m)	$CDCl_3$	484	15	80
5		8.59(1H,s),8.21(2H,d),8.06(1H,s),7.64(2H,d),5.29(2H,s),4.68(2H,s),4.20(1H,m),3.95(1H,m),3.85(1H,m),3.10(1H,m),2.80(2H,m),1.18(2H,m),1.10(2H,m)	DMSO	511	10	76
6		8.58(1H,s),8.05(1H,d),7.92-7.42(4H,m),5,28(2H,s),4.65(2H,s),4.20(1H,m),3.95(1H,m),3.78(1H,m),3.10(1H,m),2.80(2H,m),1.20(2H,m),1.09(2H,m)	DMSO	491	20	82

Table 8. (continued)

Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (min)	Yield (%)
7		8.74(1H,s),8.10(1H,d),6.92(3H,m),6.10(2H,s),5.10(2H,s),4.75(2H,s),4.30(1H,m),3.95(1H,m),3.85(1H,m),3.15(1H,m),3.10(2H,m),1.28(2H,m),1.09(2H,m)	$CDCl_3$	510	25	79
8		8.60(1H,d),8.57(1H,s),8.52(1H,d),8.03(1H,d),7.80(1H,d),7.41(1H,q),5.18(2H,s),4.65(2H,s),4.17(1H,m),3.94(1H,m),3.75(1H,m),3.30(2H,m),3.04(1H,m),2.81(1H,m),2.73(1H,m),1.30-1.00(4H,m)	DMSO $-d_6$	467	90	70
9		8.82(1H,s),8.05(1H,d),7.51(1H,d),7.45(1H,m),6.5(1H,s),5.02(2H,m),4.5(2H,m),4.20(1H,m),3.95(1H,m),3.70(1H,m),3.00(1H,m),2.80(1H,m),2.70(1H,m),1.00(4H,m)	DMSO	456	15	69
10		8.58(1H,s),8.00(1H,d),7.10(3H,m),6.72(1H,s),4.80(2H,s),4.20(1H,m),3.95(1H,m),3.85(1H,m),3.10(1H,m),2.95(2H,m),1.07(4H,m)	DMSO	542	20	65
11		8.76(1H,s),8.20(1H,m),8.02(1H,d),7.89(1H,m),7.40(1H,m),5.60(2H,s),4.78(2H,m),4.45(1H,m),3.85(1H,m),3.70(1H,m),3.10(2H,m),1.30(2H,m),1.15(2H.m)	DMSO	541	25	73

Example 12

Synthesisof7-(4-aminomethyl-3-benzyloxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid



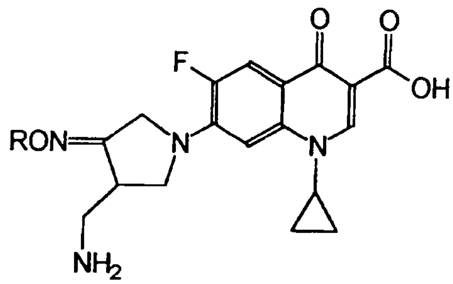
530mg of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 584mg of the compound prepared in Preparation 8 were suspended in 15ml of acetonitrile. This suspension was cooled down under ice-water bath and then 913mg of 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) was slowly added thereto. The reaction mixture was stirred for 2 hours at 80°C and, after adding 15ml of water, was then concentrated. The concentrated suspension was filtered. The filtered solid product was washed with water and ethanol to obtain 631mg (Yield: 68%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) :	δ 8.60(1H, s), 7.92(1H, d), 7.38(5H, m), 5.10(2H, s), 4.87(2H, s), 4.10(1H, m), 3.94(1H, m), 3.86(1H, m), 3.37(2H, m), 3.02(1H, m), 2.38(1H, m), 2.73-(1H, m), 1.25-1.05(4H, m)
MS (FAB, m/e) :	465(M+H)

Examples 13 to 22

The same starting material as Example 12 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 12 to prepare the respective compounds listed in the following Table 9.

Table 9. Examples 13 to 22



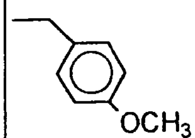
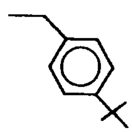
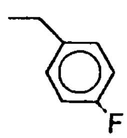
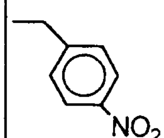
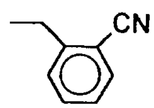
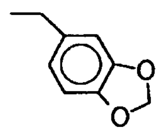
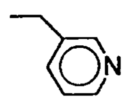
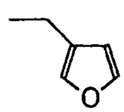
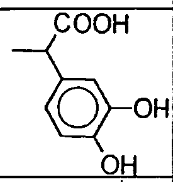
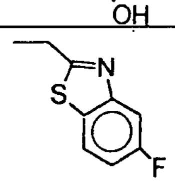
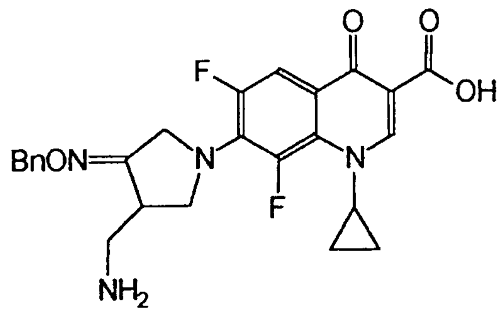
Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
13		8.6(1H,s),7.8(1H,d),7.2(3H, d),6.9(2H,d),5.1(2H,s),4.4 (2H,s),3.9(1H,m),3.8(1H,m), 3.7(3H,s),3.65(1H,m),3.0 (1H,m),2.9-2.7(2H,m),1.3-1.1(4H,m)	DMSO $-d_6$	495	2	60
14		8.6(1H,s),7.8(1H,d),7.4(2H, d),7.3(3H,m),5.1(2H,s),4.4 (2H,s),3.9(1H,m),3.8(1H,m), 3.7(1H,m),3.0(1H,m),2.9-2.7 (2H,m),1.4(9H,s),1.3-1.1 (4H,m)	DMSO $-d_6$	521	2	65
15		8.6(1H,s),7.8(1H,d),7.4(2H, m),7.2(3H,m),5.1(2H,s),4.4 (2H,s),3.9(1H,m),3.8(1H,m), 3.7(1H,m),3.0(1H,m),2.9-2.7 (2H,m),1.3-1.1(4H,m)	DMSO $-d_6$	483	4	67
16		8.6(1H,s),8.2(2H,d),7.8(1H, d),7.6(2H,d),7.2(1H,d),5.3 (2H,s),4.4(2H,s),3.9(1H,m), 3.8(1H,m),3.7(1H,m),3.0(1H, m),2.9-2.7(2H,m),1.3-1.1 (4H,m)	DMSO $-d_6$	510	3	58

Table 9. (continued)

Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
17		8.6(1H,s),7.9-7.4(5H,m),7.2(1H,d),5.3(2H,s),4.4(2H,s),3.9(1H,m),3.8(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.3-1.1(4H,m)	DMSO-d_6	490	4	55
18		8.6(1H,s),7.8(1H,d),7.2(1H,d),6.9(3H,m),6.1(2H,s),5.1(2H,s),4.4(2H,s),3.9(1H,m),3.8(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.3-1.1(4H,m)	DMSO-d_6	509	4	71
19		8.6(3H,m),7.8(2H,m),7.4(1H,q),7.2(1H,d),5.2(2H,s),4.4(1H,m),3.9(1H,m),3.8(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.3-1.1(4H,m)	DMSO-d_6	466	4	53
20		8.6(1H,s),7.8(1H,d),7.5(2H,m),7.2(1H,d),6.5(1H,m),5.0(2H,m),4.4(1H,m),3.9(1H,m),3.8(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.3-1.1(4H,m)	DMSO-d_6	455	4	60
21		8.6(1H,s),7.8(1H,d),7.2(1H,d),7.1(3H,m),6.7(1H,s),4.4(1H,m),3.9(1H,m),3.8(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.3-1.1(4H,m)	DMSO-d_6	541	4	50
22		8.6(1H,s),8.2(1H,m),7.9-7.8(2H,m),7.4(1H,m),7.2(1H,d),5.6(2H,s),4.4(1H,m),3.9(1H,m),3.8(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.3-1.1(4H,m)	DMSO-d_6	540	4	70

Example 23

Synthesis of 7-(4-aminomethyl-3-benzyloxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid



566mg of 1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 584mg of the compound prepared in Preparation 8 were suspended in 15ml of acetonitrile. This suspension was cooled down under ice-water bath and then 913mg of 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) was slowly added thereto. The reaction mixture was stirred for 2 hours at 80°C and, after adding 10ml of water, was then concentrated. The concentrated suspension was filtered. The filtered solid product was washed with water and ethanol to obtain 704mg (Yield: 73%) of the title compound.

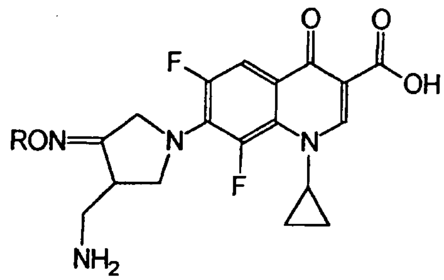
^{1}H NMR (DMSO-d_6, ppm) : δ 8.64(1H, s), 7.99(1H, d), 7.41(5H, m), 5.10(2H, s), 4.73(2H, s), 4.18(1H, m), 3.92(1H, m), 3.86(1H, m), 3.37(2H, m), 3.02(1H, m), 2.83(1H, m), 2.73-(1H, m), 1.25-1.05(4H, m)

MS (FAB, m/e) : 483(M + H)

Examples 24 to 33

The same starting material as Example 23 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 23 to prepare the respective compounds listed in the following Table 10.

Table 10. Examples 24 to 33



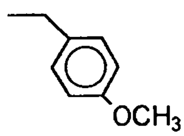
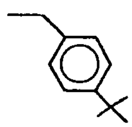
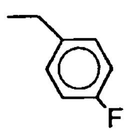
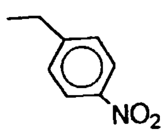
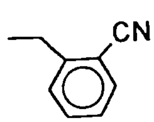
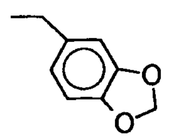
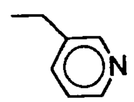
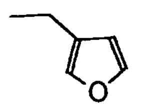
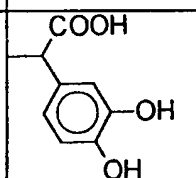
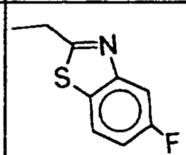
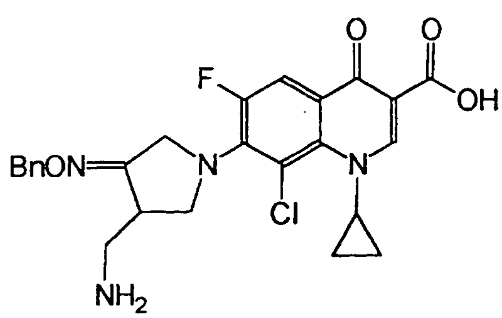
Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
24		8.6(1H,s),7.7(1H,d),7.2(2H,d),6.9(2H,d),5.1(2H,s),4.3(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),3.7(3H,s),2.9(1H,m),2.8-2.7(2H,m),1.15(4H,m)	DMSO $-d_6$	513	2	75
25		8.6(1H,s),7.7(1H,d),7.5(2H,m),7.1(2H,m),5.1(2H,s),4.3(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),2.9(1H,m),2.8-2.7(2H,m),1.4(9H,s),1.15(4H,m)	DMSO $-d_6$	539	4	70
26		8.6(1H,s),7.7(1H,d),7.3(2H,m),7.1(2H,m),5.1(2H,s),4.3(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),2.9(1H,m),2.8-2.7(2H,m),1.15(4H,m)	DMSO $-d_6$	501	4	80
27		8.6(1H,s),8.2(2H,d),7.7(1H,d),7.6(2H,d),5.3(2H,s),4.3(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),2.9(1H,m),2.8-2.7(2H,m),1.15(4H,m)	DMSO $-d_6$	528	3	68
28		8.6(1H,s),7.9-7.4(5H,m),5.3(2H,s),4.3(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),2.9(1H,m),2.8-2.7(2H,m),1.15(4H,m)	DMSO $-d_6$	508	2	70

Table 10. (continued)

Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
29		8.6(1H,s),7.7(1H,d),7.0(3H,m),6.1(2H,s),5.1(2H,s),4.3(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),2.9(1H,m),2.8-2.7(2H,m),1.15(4H,m)	DMSO $-d_6$	527	3	69
30		8.6(3H,m),7.8(1H,d),7.7(1H,d),7.4(1H,q),5.3(2H,s),4.3(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),2.9(1H,m),2.8-2.7(2H,m),1.15(4H,m)	DMSO $-d_6$	484	3	58
31		8.6(1H,s),7.7(1H,d),7.5(2H,m),6.5(1H,m),5.0(2H,m),4.3(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),2.9(1H,m),2.8-2.7(2H,m),1.15(4H,m)	DMSO $-d_6$	473	3	70
32		8.6(1H,s),7.7(1H,d),7.1(3H,m),6.6(1H,s),4.3(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),2.9(1H,m),2.8-2.7(2H,m),1.15(4H,m)	DMSO $-d_6$	559	4	59
33		8.6(1H,s),8.3(1H,m),7.9(1H,m),7.7(1H,d),7.4(1H,m),5.6(2H,s),4.3(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),2.9(1H,m),2.8-2.7(2H,m),1.15(4H,m)	DMSO $-d_6$	558	4	60

Example 34

Synthesis of 7-(4-aminomethyl-3-benzyloxyimino-pyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid



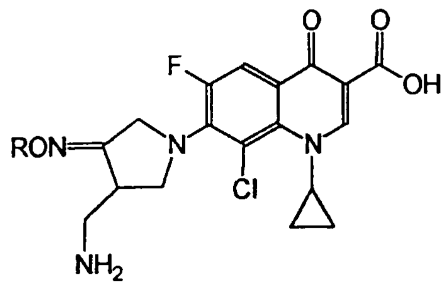
598mg of 8-chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 584mg of the compound prepared in Preparation 8 were suspended in 15ml of acetonitrile and then 913mg of 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) was slowly added thereto. The reaction mixture was stirred for 3 hours at 80°Cand, after adding 15ml of water, was then concentrated. The concentrated suspension was filtered. The filtered solid product was washed with water and ethyl ether to obtain 510mg (Yield: 52%) of the title compound.

^1H NMR ($DMSO-d_6$, ppm) :	δ 8.78(1H, s), 7.91(1H, d), 7.41(5H, m), 5.16(2H, s), 4.74(2H, s), 4.16(1H, m), 3.90(1H, m), 3.85(1H, m), 3.35(2H, m), 3.02(1H, m), 2.82(1H, m), 2.75-(1H, m), 1.30-1.10(4H, m)
MS (FAB, m/e) :	499(M + H)

Examples 35 to 44

The same starting material as Example 34 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 34 to prepare the respective compounds listed in the following Table 11.

Table 11. Examples 35 to 44



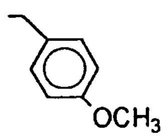
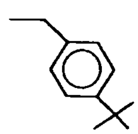
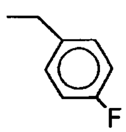
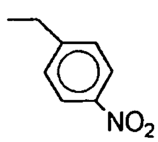
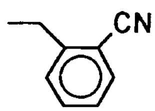
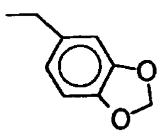
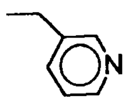
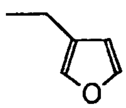
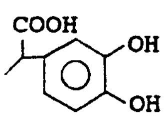
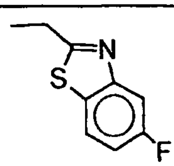
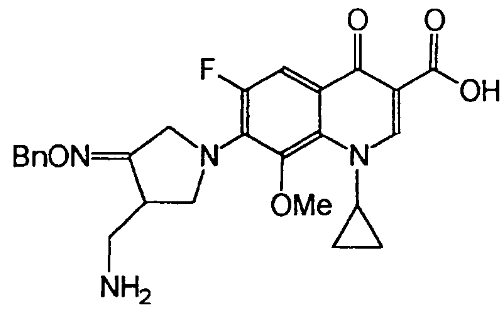
Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
35		8.7(1H,s),7.9(1H,d),7.3(2H,d),7.0(2H,d),5.1(2H,s),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.7(3H,s),3.0(1H,m),2.9-2.6(2H,s),1.2-0.9(4H,m)	DMSO $-d_6$	529	3	63
36		8.7(1H,s),7.9(1H,d),7.5(2H,d),7.3(2H,d),5.2(2H,s),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.4(9H,s),1.2-0.9(4H,m)	DMSO $-d_6$	555	3	73
37		8.7(1H,s),7.9(1H,d),7.4(2H,m),7.1(2H,m),5.1(2H,s),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.2-0.9(4H,m)	DMSO $-d_6$	517	2	80
38		8.7(1H,s),8.3(2H,d),7.9(1H,d),7.7(2H,d),5.4(2H,s),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.2-0.9(4H,m)	DMSO $-d_6$	544	4	63

Table 11. (continued)

Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
39		8.7(1H,s),7.9-7.4(5H,m),5.3(2H,s),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.2-0.9(4H,m)	DMSO-d_6	524	4	70
40		8.7(1H,s),7.9(1H,d),7.0(3H,m),6.1(2H,s),5.1(2H,s),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.2-0.9(4H,m)	DMSO-d_6	543	2	67
41		8.7(1H,s),7.9(1H,d),8.6(2H,m),7.8(1H,d),7.4(1H,q),5.2(2H,s),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.2-0.9(4H,m)	DMSO-d_6	500	4	60
42		8.7(1H,s),7.9(1H,d),7.5(2H,m),6.5(1H,m),5.0(2H,m),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.2-0.9(4H,m)	DMSO-d_6	489	2	62
43		8.7(1H,s),7.9(1H,d),7.1(3H,m),6.7(1H,s),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.0(1H,m),2.9-2.6(2H,m),1.2-0.9(4H,m)	DMSO-d_6	575	4	60
44		8.7(1H,s),8.2(1H,m),7.9(2H,m),7.4(1H,m),5.6(2H,s),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.2-0.9(4H,m)	DMSO-d_6	574	4	76

Example 45

Synthesis of 7-(4-aminomethyl-3-benzyloxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid



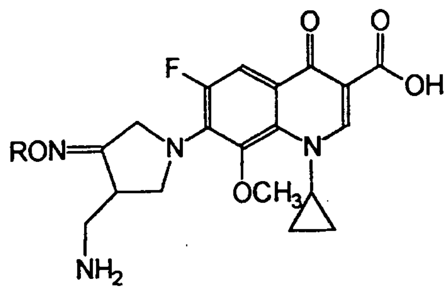
590mg of 1-cyclopropyl-6,7-difluoro-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylic acid and 584mg of the compound prepared in Preparation 8 were suspended in 15ml of acetonitrile and then 913mg of 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) was slowly added thereto. The reaction mixture was stirred for 2 hours at 80°Cand, after adding 15ml of water, was then stirred for 30 minutes at room temperature and filtered. The filtered solid product was washed with water and ethyl ether to obtain 465mg (Yield: 47%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) :	δ 8.61(1H, s), 7.99(1H, d), 7.40(5H, m), 5.15(2H, s), 4.74(2H, s), 4.17(1H, m), 3.95(1H, m), 3.83(1H, m), 3.60(3H, s), 3.35(2H, m), 3.02(1H, m), 2.80-(1H, m), 2.71(1H, m), 1.30-1.10(4H, m)
MS (FAB, m/e) :	495(M + H)

Examples 46 to 55

The same starting material as Example 45 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 45 to prepare the respective compounds listed in the following Table 12.

Table 12. Examples 46 to 55



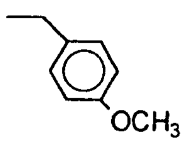
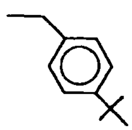
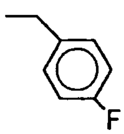
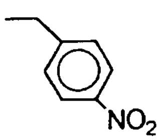
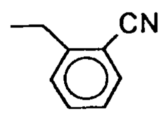
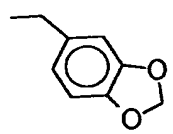
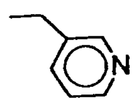
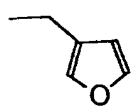
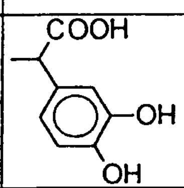
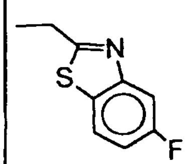
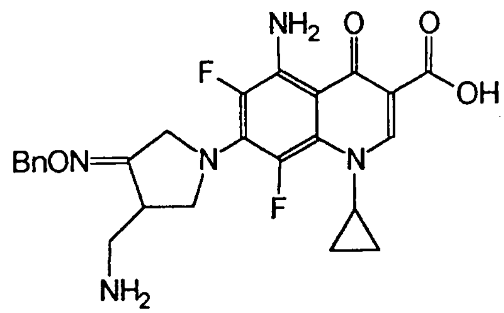
Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
46		8.8(1H,s),7.8(1H,d),7.4(2H,d),7.1(2H,d),5.2(2H,s),4.6(2H,s),4.3(1H,m),4.1(1H,m),3.9(1H,m),3.8(3H,s),3.0(1H,m),2.9-2.7(2H,m),2.7(3H,s),1.3(2H,m),0.95(2H,m)	DMSO $-d_6$	525	17	38
47		8.8(1H,s),7.8(1H,d),7.6(2H,d),7.4(2H,d),5.3(2H,s),4.6(2H,s),4.3(1H,m),4.1(1H,m),3.9(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.7(3H,s),1.5(9H,s),1.3(2H,m),0.95(2H,m)	DMSO $-d_6$	551	17	34
48		8.8(1H,s),7.8(1H,d),7.5(2H,m),7.2(2H,m),5.2(2H,s),4.6(2H,s),4.3(1H,m),4.1(1H,m),3.9(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.7(3H,s),1.3(2H,m),0.95(2H,m)	DMSO $-d_6$	513	17	40
49		8.8(1H,s),8.3(2H,d),7.8(1H,d),7.7(2H,d),5.4(2H,s),4.6(2H,s),4.3(1H,m),4.1(1H,m),3.9(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.7(3H,s),1.3(2H,m),0.95(2H,m)	DMSO $-d_6$	540	17	37

Table 12. (continued)

Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
50		8.8(1H,s),8.0-7.5(5H,m),5.4(2H,s),4.6(2H,s),4.3(1H,m),4.1(1H,m),3.9(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.7(3H,s),1.3(2H,m),0.95(2H,m)	DMSO $-d_6$	520	17	42
51		8.8(1H,s),7.8(1H,d),7.0(3H,m),6.2(2H,s),5.2(2H,s),4.6(2H,s),4.3(1H,m),4.1(1H,m),3.9(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.7(3H,s),1.3(2H,m),0.95(2H,m)	DMSO $-d_6$	539	17	44
52		8.8(1H,s),8.6(2H,m),7.9(1H,d),7.8(1H,d),7.4(1H,q),5.3(2H,s),4.6(2H,s),4.3(1H,m),4.1(1H,m),3.9(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.7(3H,s),1.3(2H,m),0.95(2H,m)	DMSO $-d_6$	496	17	30
53		8.8(1H,s),7.8(1H,d),7.6(2H,m),6.5(1H,m),5.1(2H,m),4.6(2H,s),4.3(1H,m),4.1(1H,m),3.9(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.7(3H,s),1.3(2H,m),0.95(2H,m)	DMSO $-d_6$	485	17	29
54		8.8(1H,s),7.8(1H,d),7.2(3H,m),6.8(1H,s),4.6(2H,s),4.3(1H,m),4.1(1H,m),3.9(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.7(3H,s),1.3(2H,m),0.95(2H,m)	DMSO $-d_6$	571	20	27
55		8.8(1H,s),8.3(1H,m),8.0(1H,m),7.8(1H,d),7.5(1H,m),5.7(2H,s),4.6(2H,s),4.3(1H,m),4.1(1H,m),3.9(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.7(3H,s),1.3(2H,m),0.95(2H,m)	DMSO $-d_6$	570	17	42

Example 56

Synthesis of 5-amino-7-(4-aminomethyl-3-benzyloxyimino-pyrrolidin -1-yl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid



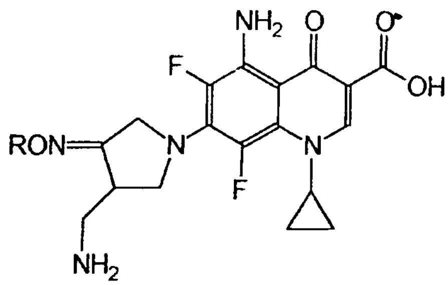
448mg of 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro4-oxoquinoline-3-carboxylic acid and 438mg of the compound prepared in Preparation 8 were suspended in 15ml of acetonitrile and then 685mg of 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) was slowly added thereto. The reaction mixture was heated for 6 hours at 80°C and 10ml of water was added thereto. This suspension was filtered. The filtered solid product was washed with water, acetonitrile and ethyl ether to obtain 395mg (Yield: 53%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) :	δ 8.62(1H, s), 7.92(1H, d), 7.40(5H, m), 6.10(2H, bs), 5.13(2H, s), 4.73(2H, s), 4.15(1H, m), 3.95(1H, m), 3.82(1H, m), 3.35(2H, m), 3.01(1H, m), 2.80-(1H, m), 2.73(1H, m), 1.25-1.05(4H, m)
MS (FAB, m/e) :	498(M+H)

Examples 57 to 66

The same starting material as Example 56 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 56 to prepare the respective compounds listed in the following Table 13.

Table 13. Examples 57 to 66



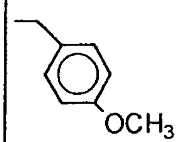
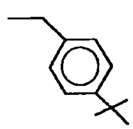
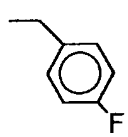
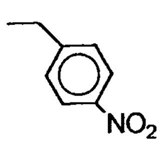
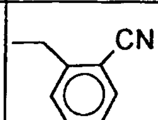
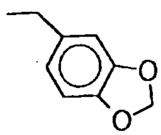
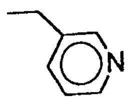
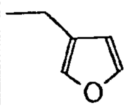
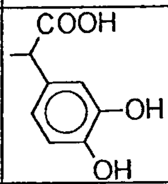
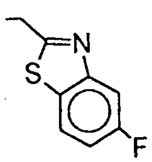
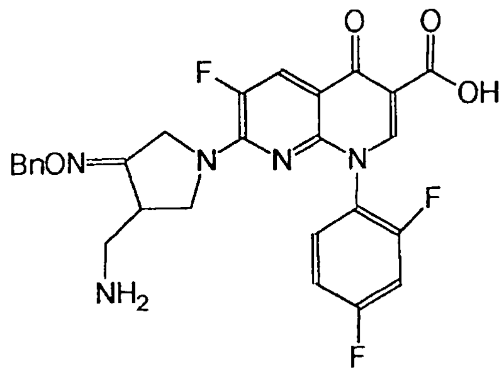
Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
57		8.4(1H,s),7.4(2H,bs),7.2 (2H,d),7.0(2H,d),5.1(2H,s), 4.6(2H,m),4.2(1H,m),3.9(1H, m),3.8(3H,s),3.7(1H,m),3.0 (1H,m),2.8-2.6(2H,m),1.1 (4H,s)	DMSO $-d_6$	528	10	59
58		8.4(1H,s),7.5(2H,d),7.4(2H, bs),7.3(2H,d),5.2(2H,s),4.6 (2H,m),4.2(1H,m),3.9(1H,m), 3.7(1H,m),3.0(1H,m),2.8-2.6 (2H,m),1.4(9H,s),1.1(4H,s)	DMSO $-d_6$	554	17	67
59		8.4(1H,s),7.4(4H,m),7.1(2H, m),5.1(2H,s),4.6(2H,m),4.2 (1H,m),3.9(1H,m),3.7(1H,m), 3.0(1H,m),2.8-2.6(2H,m),1.1 (4H,s)	DMSO $-d_6$	516	17	55
60		8.4(1H,s),8.2(2H,d),7.6(2H, d),7.4(2H,bs),5.3(2H,s),4.6 (2H,m),4.2(1H,m),3.9(1H,m), 3.7(1H,m),3.0(1H,m),2.8-2.6 (2H,m),1.1(4H,s)	DMSO $-d_6$	543	17	56
61		8.4(1H,s),7.9-7.4(6H,m),5.3 (2H,s),4.6(2H,m),4.2(1H,m), 3.9(1H,m),3.7(1H,m),3.0(1H, m),2.8-2.6(2H,m),1.1(4H,s)	DMSO -d6	523	18	62

Table 13. (continued)

Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
62		8.4(1H,s),7.3(2H,bs),7.0(3H,m),6.2(2H,s),5.2(2H,s),4.6(2H,m),4.2(1H,m),3.9(1H,m),3.7(1H,m),3.0(1H,m),2.8-2.6(2H,m),1.1(4H,s)	DMSO $-d_6$	542	18	65
63		8.5(3H,m),7.6(1H,d),7.4(1H,q),7.3(2H,bs),5.3(2H,s),4.6(2H,m),4.2(1H,m),3.9(1H,m),3.7(1H,m),3.0(1H,m),2.8-2.6(2H,m),1.1(4H,s)	DMSO $-d_6$	499	17	52
64		8.4(1H,s),7.5-7.4(4H,m),6.5(1H,m),5.0(2H,m),4.6(2H,m),4.2(1H,m),3.9(1H,m),3.7(1H,m),3.0(1H,m),2.8-2.6(2H,m),1.1(4H,s)	DMSO $-d_6$	488	18	49
65		8.4(1H,s),7.4(2H,bs),7.1(3H,m),6.7(1H,s),4.6(2H,m),4.2(1H,m),3.9(1H,m),3.7(1H,m),3.0(1H,m),2.8-2.6(2H),1.1(4H,s)	DMSO $-d_6$	574	18	43
66		8.4(1H,s),8.2(1H,m),7.9(1H,m),7.4(3H,m),5.6(2H,s),4.6(2H,m),4.2(1H,m),3.9(1H,m),3.7(1H,m),3.0(1H,m),2.8-2.6(2H,m),1.1(4H,s)	DMSO $-d_6$	573	17	65

Example 67

Synthesis of 7-(4-aminomethyl-3-benzyloxyimino-pyrrolidin-1-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid



806mg of 7-chloro-1(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid and 438mg of the compound prepared in Preparation 8 were suspended in 15ml of acetonitrile and then 913mg of 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) was slowly added thereto. The reaction mixture was stirred for one hour at room temperature, and after adding 15ml of water, was then stirred for further 30 minutes and filtered. The filtered solid product was washed with water and acetonitrile to obtain 524mg (Yield: 65%) of the title compound.

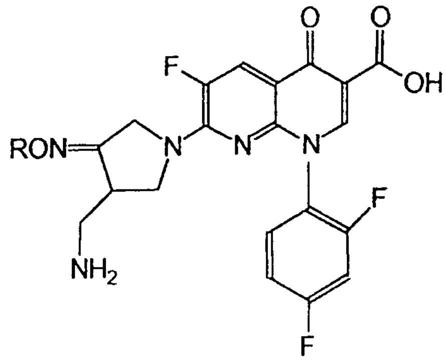
^{1}H NMR (DMSO-d_6, ppm) : δ 8.82(1H, s), 8.21(1H, d), 7.85(1H, m), 7.56(1H, m), 7.40(6H, m), 5.16(2H, s), 4.76(2H, s), 4.18(1H, m), 3.94(1H, m), 3.81(1H, m), 3.34(2H, m), 3.04-(1H, m), 2.82(1H, m), 2.73(1H, m), 1.30-1.00(4H, m)

MS (FAB, m/e) : 538(M+H)

Examples 68 to 77

The same starting material as Example 67 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 67 to prepare the respective compounds listed in the following Table 14.

Table 14. Examples 68 to 77



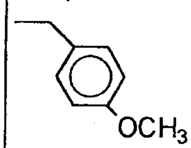
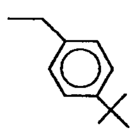
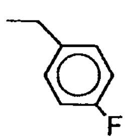
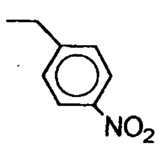
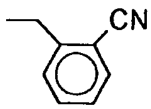
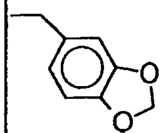
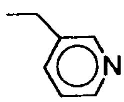
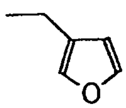
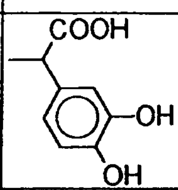
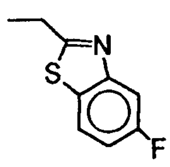
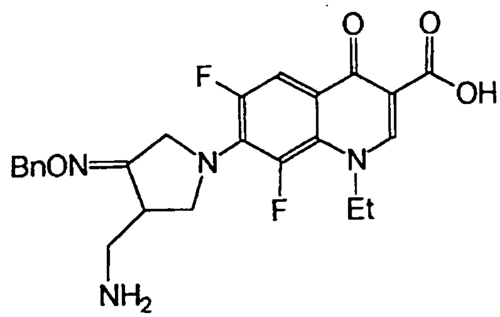
Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (min)	Yield (%)
68		8.9(1H,s),8.1(1H,d),7.8(1H,m),7.6(1H,dd),7.3(3H,m),7.1(2H,d),5.2(2H,s),4.3(2H,s),4.0(1H,m),3.9(1H,m),3.8(3H,s),3.0(1H,m),2.8-2.6(2H,m)	DMSO $-d_6$	568	20	78
69		8.9(1H,s),8.1(1H,d),7.8(1H,m),7.6(2H,m),7.3(2H,m),5.2(2H,s),4.3(2H,s),3.9(1H,m),3.0(1H,m),2.8-2.6(2H,m),1.5(9H,s)	DMSO $-d_6$	594	10	80
70		8.9(1H,s),8.1(1H,d),7.8(1H,m),7.6(1H,dd),7.4(2H,m),7.3(1H,dd),7.1(2H,m),5.1(2H,s),4.3(2H,s),4.0(1H,m),3.9(1H,m),3.0(1H,m),2.8-2.6(2H,m)	DMSO $-d_6$	556	15	81
71		8.9(1H,s),8.3(2H,d),8.1(1H,d),7.8(1H,m),7.7(2H,d),7.6(1H,dd),7.3(1H,m),5.3(2H,s),4.3(2H,s),4.0(1H,m),3.9(1H,m),3.0(1H,m),2.8-2.6(2H,m)	DMSO $-d_6$	583	15	75

Table 14. (continued)

Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (min)	Yield (%)
72		8.8(1H,s),8.1(1H,d),7.9-7.4(6H,m),7.3(1H,dd),5.3(2H,s),4.3(2H,s),4.0(1H,m),3.9(1H,m),3.0(1H,m),2.8-2.6(2H,m)	DMSO $-d_6$	563	15	80
73		8.8(1H,s),8.1(1H,d),7.8(1H,m),7.6(1H,dd),7.3(1H,dd),7.0(3H,m),6.2(2H,s),5.1(2H,s),4.3(2H,s),4.0(1H,m),3.9(1H,m),3.0(1H,m),2.8-2.6(2H,m)	DMSO $-d_6$	582	15	87
74		8.8(1H,s),8.6(1H,s),8.5(1H,q),7.8(2H,m),7.6(1H,dd),7.4(1H,q),7.3(1H,dd),5.2(2H,s),4.3(2H,s),4.0(1H,m),3.9(1H,m),3.0(1H,m),2.8-2.6(2H,m)	DMSO $-d_6$	539	15	70
75		8.8(1H,s),8.1(1H,d),7.8(1H,m),7.6(1H,dd),7.5(1H,d),7.45(1H,dd),6.6(1H,m),5.0(2H,m),4.3(2H,s),4.0(1H,m),3.9(1H,m),3.0(1H,m),2.8-2.6(2H,m)	DMSO $-d_6$	528	10	69
76		8.8(1H,s),8.1(1H,d),7.8(1H,m),7.6(1H,dd),7.3(1H,dd),7.1(3H,m),6.7(1H,s),4.3(2H,s),4.0(1H,m),3.9(1H,m),3.0(1H,m),2.8-2.6(2H,m)	DMSO $-d_6$	614	20	59
77		8.8(1H,s),8.2(1H,m),8.1(1H,d),8.0(1H,m),7.8(1H,d),7.6(1H,dd),7.4(1H,m),7.3(1H,dd),5.6(2H,s),4.3(2H,s),4.0(1H,m),3.9(1H,m),3.0(1H,m),2.8-2.6(2H,m)	DMSO $-d_6$	613	10	82

Example 78

Synthesis of 7-(4-aminomethyl-3-benzyloxyiminopyrrolidin-1-yl)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid



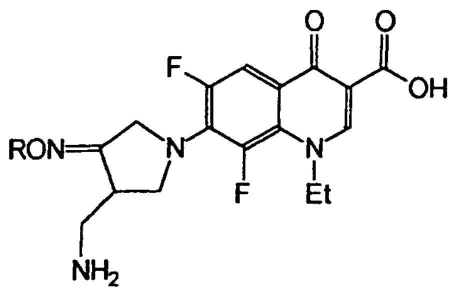
353mg of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline3-carboxylic acid and 380mg of the compound prepared in Preparation 8 were suspended in 15ml of acetonitrile and then 593mg of 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) was slowly added thereto. The reaction mixture was stirred for 2.5 hours at 80°C, and after adding 15ml of water, was then stirred for further 30 minutes under cold water bath and filtered. The filtered solid product was washed with water, acetonitrile and ethyl ether to obtain 391mg (Yield: 64%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) :	δ 8.8(1H, s), 7.8(1H, d), 7.40(5H, m), 5.10(2H,s), 4.6(2H, q), 4.4(2H, dd), 4.0(1H, m), 3.7(1H, m), 3.1(1H, m), 2.8(2H, ddd), 1.46(3H, t)
MS (FAB, m/e) :	471(M + H)

Examples 79 to 88

The same starting material as Example 78 was reacted with each of the compounds prepared in Preparations 19 to 28 according to the same procedure as Example 78 to prepare the respective compounds listed in the following Table 15.

Table 15. Examples 79 to 88



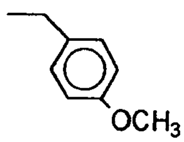
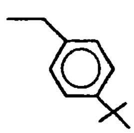
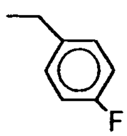
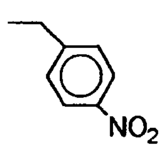
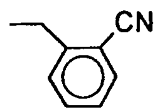
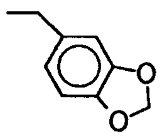
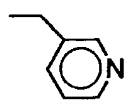
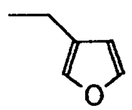
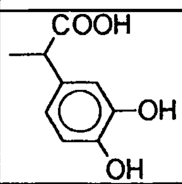
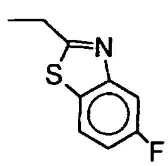
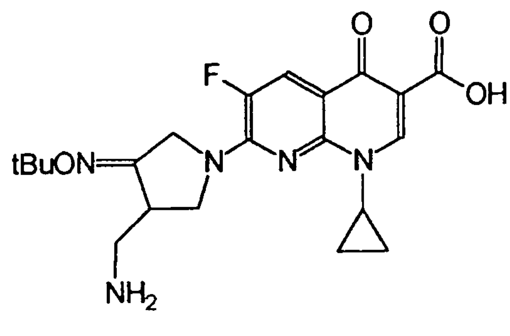
Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
79		8.8(1H,s),7.8(1H,d),7.4(2H,d),7.1(2H,d),5.0(2H,s),4.5(2H,q),4.4(2H,s),4.2(1H,m),3.9(1H,m),3.7(3H,s),3.1(1H,m),2.9-2.7(2H,m),1.45(3H,t)	DMSO-d_6	501	4	73
80		8.8(1H,s),7.8(1H,d),7.4(2H,d),7.2(2H,d),5.1(2H,s),4.5(2H,q),4.4(2H,s),4.1(1H,m),3.9(1H,m),3.1(1H,m),2.9-2.7(2H,m),1.45(3H,t),1.4(9H,s)	DMSO-d_6	527	2.5	77
81		8.8(1H,s),7.8(1H,d),7.3(2H,m),7.0(2H,m),5.0(2H,s),4.5(2H,q),4.4(2H,s),4.2(1H,m),3.9(1H,m),3.1(1H,m),2.9-2.7(2H,m),1.45(3H,t)	DMSO-d_6	489	3	80
82		8.8(1H,s),8.3(2H,d),7.8(1H,d),7.7(2H,d),5.3(2H,s),4.5(2H,q),4.4(2H,s),4.2(1H,m),3.9(1H,m),3.1(1H,m),2.9-2.7(2H,m),1.45(3H,t)	DMSO-d_6	516	3	75

Table 15. (continued)

Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
83		8.8(1H,s),7.9-7.4(5H,m),5.3(2H,s),4.5(2H,q),4.4(2H,s),4.2(1H,m),3.9(1H,m),3.1(1H,m),2.9-2.7(2H,m),1.45(3H,t)	DMSO $-d_6$	496	3	80
84		8.8(1H,s),7.8(1H,d),6.8(3H,m),6.0(2H,s),5.0(2H,s),4.5(2H,q),4.4(2H,s),4.2(1H,m),3.9(1H,m),3.1(1H,m),2.9-2.7(2H,m),1.45(3H,t)	DMSO $-d_6$	515	4	69
85		8.8(1H,s),8.6(2H,m),7.8(2H,m),7.4(1H,q),5.3(2H,s),4.5(2H,q),4.4(2H,s),4.2(1H,m),3.9(1H,m),3.1(1H,m),2.9-2.7(2H,m),1.45(3H,t)	DMSO $-d_6$	471	2	70
86		8.8(1H,s),7.8(1H,d),7.5(2H,m),6.5(1H,m),5.0(2H,m),4.5(2H,q),4.4(2H,s),4.2(1H,m),2.9(1H,m),3.1(1H,m),2.9-2.7(2H,m),1.45(3H,t)	DMSO $-d_6$	461	2	67
87		8.8(1H,s),7.8(1H,d),7.1(3H,m),6.7(1H,s),4.5(2H,q),4.4(2H,s),4.2(1H,m),3.9(1H,m),3.1(1H,m),2.9-2.7(2H,m),1.45(3H,t)	DMSO $-d_6$	547	3	63
88		8.8(1H,s),8.2(1H,m),7.9(1H,m),7.8(1H,d),7.4(1H,m),5.6(2H,s),4.5(2H,q),4.4(2H,s),4.2(1H,m),3.9(1H,m),3.1(1H,m),2.9-2.7(2H,m),1.5(3H,t)	DMSO $-d_6$	546	4	70

Example 89

Synthesis of 7-(4-aminomethyl-3-t-butyloxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid



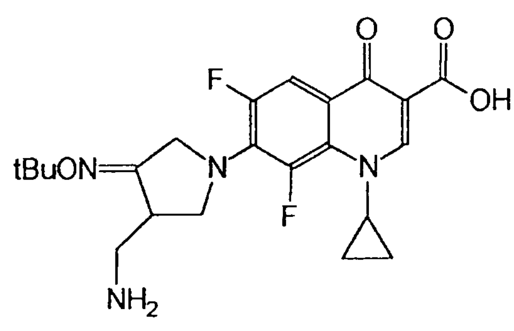
141mg (0.5 mmole) of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid and 143mg (0.55 mmole) of 4-aminomethyl-pyrrolidin-3-one t-butyloxime dihydrochloride were thoroughly suspended in 2.5ml of acetonitrile. Then, 230mg (1.5 mmole) of 1,8-diazabicyclo[5.4.0]undec-7-ene was slowly added dropwise thereto. The reaction mixture was stirred for 30 minutes at room temperature, and after adding 1ml of water, was then vigorously stirred for 10 minutes and filtered. The filtered solid product was successively washed with acetonitrile-water (4:1 v/v, 2ml) and acetonitrile (2mlX2) and then with ether and dried to obtain 132mg (Yield: 61%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) : δ 8.6(1H, s), 8.1(1H, d), 4.6(2H, s), 4.2(1H, dd), 3.9(1H, dd), 3.7(1H, m), 3.1(1H, dd), 2.9-2.7(2H, ddd), 1.3(9H, s), 1.2(2H, m), 1.1(2H, m)

FAB MS (POS) : 432[M+H]$^+$

Example 90

Synthesis of 7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic aicd



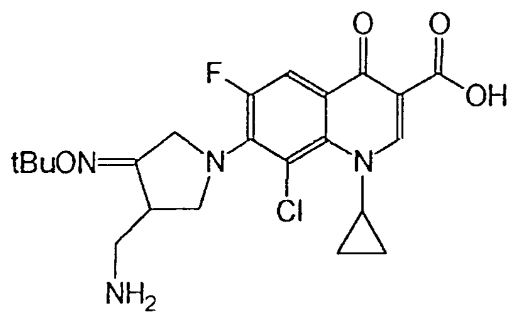
141mg (0.5 mmole) of 1-cyclopropyl-6,7,8-trifluoro-4-oxo-1,4 -dihydroquinoline-3-carboxylic acid and 143mg (0.55 mmole) of 3-aminomethyl-4-t-butyloxyiminopyrrolidine dihydrochloride were refluxed for 2.5 hours under heating according to the same manner as Example 89 and cooled down to room temperature. Then, the resulting product was then separated and purified with preparative HPLC to obtain 151mg (Yield: 67%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) : δ 8.8(1H, s), 7.8(1H, d), 4.5(2H, s), 4.3(1H, m), 3.9(1H, m), 3.8(1H, m), 2.9-(1H, m), 2.8-2.7(2H, m), 1.3(9H, s), 1.15(4H, s)

FAB MS(POS) : 449[M+H]$^+$

Example 91

Synthesis of 8-chloro-1-cyclopropyl-6-fluoro-[7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



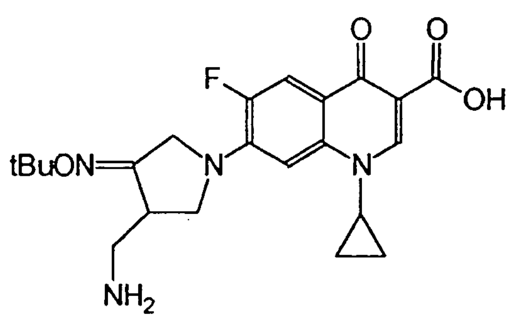
150mg (0.5 mmole) of 8-chloro-1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was reacted according to the same manner as Example 90. Then, the reaction solution was concentrated and the residue was purified with preparative HPLC to obtain 148mg (Yield: 64%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) : δ 8.7(1H, s), 7.9(1H, d), 4.4(2H, s), 4.3(1H, m), 3.8(1H, m), 3.7(1H, m), 3.0-(1H, m), 2.9-2.7(2H, m), 1.3(9H, s), 1.2-0.9(4H, m)

FAB MS(POS) : $[M+H]^+$ = 465

Example 92

Synthesisof7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



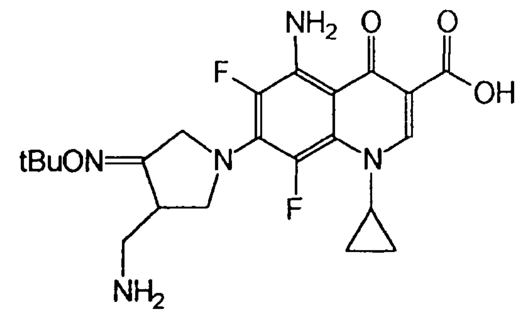
132mg (0.5 mmole) of 1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was refluxed for 3.5 hours under heating according to the same manner as Example 89. Then, the resulting residue was subjected to preparative HPLC to obtain 129mg (Yield: 60%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) : δ 8.6(1H, s), 7.8(1H, d), 7.2(1H, d), 4.4(2H, s), 3.9(1H, m), 3.8(1H, m), 3.7-(1H, m), 3.0(1H, m), 2.9-2.7(2H, m), 1.4(9H, s), 1.3-1.1(4H, m)

FAB MS(POS) : $[M+H]^+$ = 431

Example 93

Synthesis of 5-amino-7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



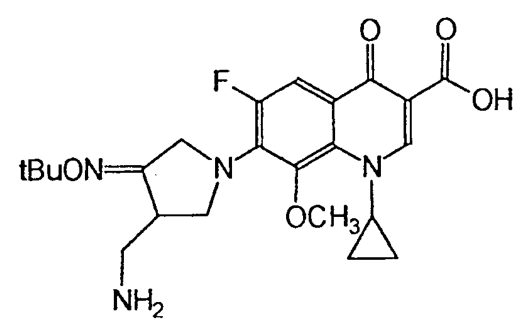
148mg (0.5 mmole) of 5-amino-1-cyclopropyl-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was refluxed for 8 hours under heating according to the same manner as Example 89. Then, the resulting residue was purified with preparative HPLC to obtain 151mg (Yield: 65%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) : δ 8.6(1H, s), 7.5(2H, br), 4.3(2H, s), 4.0-3.8(3H, m), 3.2(1H, m), 2.8-2.6(2H, m), 1.3(9H, s), 1.1(4H, m)

FAB MS(POS) : $[M+H]^+$ = 464

Example 94

Synthesis of 7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



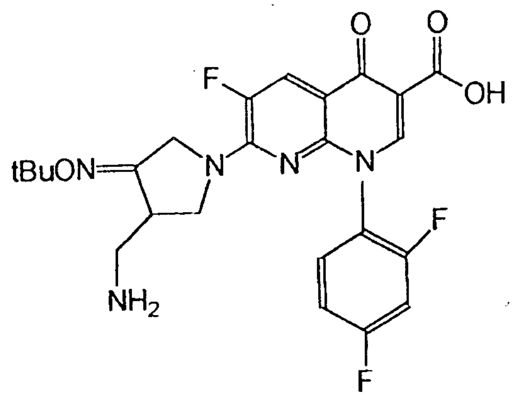
148mg (0.5 mmole) of 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was refluxed for 10 hours under heating according to the same manner as Example 89. Then, the resulting residue was purified with preparative HPLC to obtain 92mg (Yield: 40%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) : δ 8.9(1H, s), 7.8(1H, d), 4.5(2H, s), 4.3(1H, m), 4.1(1H, m), 3.9(1H, m), 3.0-(1H, m), 2.8-2.7(2H, m), 2.7(3H, s), 1.3(9H, s), 1.25(2H, m), 0.9(2H, s)

FAB MS(POS) : $[M+H]^+$ = 461

Example 95

Synthesis of 7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid



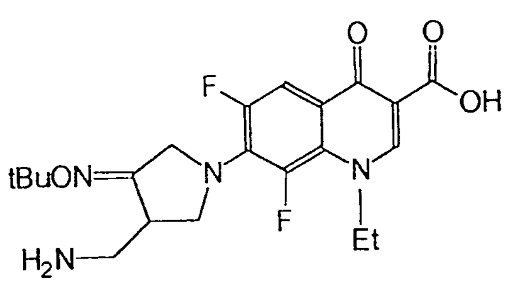
168mg (0.5 mmole) of 6,7-difluoro-1-(2,4-difluorophenyl)-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid and 143mg (0.55 mmole) of 3-aminomethyl-4-t-butyloxyiminopyrrolidine dihydrochloride were suspended in 3ml of dry acetonitrile. Then, 230mg (1.5 mmole) of 1,8-diazabicyclo[5.4.0]undec-7-ene was added thereto, and the reaction mixture was stirred for 15 minutes at room temperature and then treated according to the same manner as Example 89 to obtain 203mg (Yield: 81%) of the title compound.

^1H NMR (DMSO-d_6, ppm) : δ 8.9(1H, s), 8.1(1H, d), 7.8(1H, m), 7.6(1H, dd), 7.3(1H, dd), 4.3(2H, s), 4.0(1H, m), 3.9(1H, m), 3.0(1H, m), 2.8-2.6(2H, m), 1.3(9H, s)

FAB MS(POS) : $[M+H]^+$ = 504

Example 96

Synthesis of 7-(3-aminomethyl-4-t-butyloxyiminopyrrolidin-1-yl)-6,8-difluoro-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



136mg (0.5 mmole) of 1-ethyl-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was refluxed for 5 hours under heating according to the same manner as Example 89. Then, the resulting residue was purified with preparative HPLC to obtain 170mg (Yield: 78%) of the title compound.

^1H NMR (DMSO-d_6, ppm) : δ 8.8(1H, s), 7.8(1H, d), 4.5(2H, q), 4.4(2H, s), 4.2(1H, m), 3.9(1H, m), 3.1-(1H, m), 2.9-2.7(2H, m), 1.45(3H, t), 1.3(9H, s)

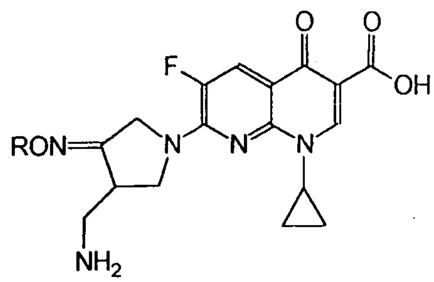
FAB MS(POS) : $[M+H]^+$ = 437

Examples 97 to 176

The amine compounds prepared in Preparations 41 to 50 were treated according to the same procedure as Examples 89 to 96 to prepare the respective compounds 97 to 176 of which NMR and MS

data are listed in the following Tables 16 to 23.

Table 16. Examples 97 to 106



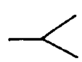
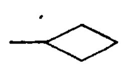
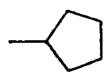
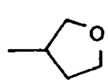
Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (min)	Yield (%)
97		8.6(1H,s),8.0(1H,d),4.7(1H,m),4.6(2H,s),4.2(1H,m),3.9(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.2-1.0(4H,m),0.9(6H,d)	DMSO-d_6	418	10	73
98		8.6(1H,s),8.05(1H,d),4.8(1H,m),4.7(2H,s),4.2(1H,m),4.0(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.2(2H,m),2.1(2H,m),1.7(1H,m),1.5(1H,m),1.2-1.0(4H,m)	DMSO-d_6	430	10	63
99		8.6(1H,s),8.0(1H,d),4.7(1H,m),4.5(2H,s),4.2(1H,m),3.9(1H,m),3.7(1H,m),3.1(1H,m),2.9-2.8(2H,m),1.7(4H,s),1.6(2H,m),1.5(2H,m),1.2-1.0(4H,m)	DMSO-d_6	444	50	77
100		8.6(1H,s),8.0(1H,d),4.8(1H,m),4.6(2H,s),4.2(1H,m),3.9(1H,m),3.8-3.6(5H,m),3.1(1H,m),2.9-2.7(2H,m),2.3-1.9(2H,m),1.2-1.0(4H,m)	DMSO-d_6	446	30	61
101		8.65(1H,s),8.05(1H,d),4.6(2H,s),4.25(1H,m),3.9(1H,m),3.85(2H,dd),3.75(1H,m),3.1(1H,m),3.0-2.8(2H,m),1.3-1.0(5H,m),0.5(2H,m),0.3(2H,m)	DMSO-d_6	430	30	84

Table 16. (continued)

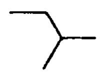
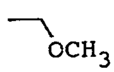
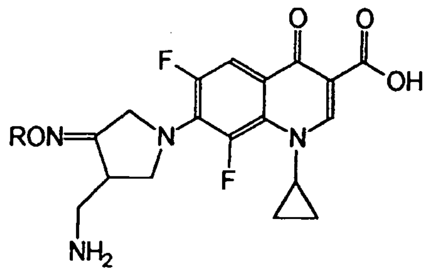
Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (min)	Yield (%)
102		8.6(1H,s),8.0(1H,d),4.6(2H,s),4.2(1H,m),3.95(1H,m),3.8(2H,d),3.7(1H,m),3.05(1H,m),2.9-2.7(2H,m),1.9(1H,m),1.2-1.0(4H,m),0.9(6H,d)	DMSO $-d_6$	432	15	80
103		8.60(1H,s),8.05(1H,d),4.74(2H,s),4.60(2H,s),4.21(1H,m),3.97(1H,m),3.75(1H,m),3.50(1H,s),3.35(2H,s),3.08(1H,m),2.90-2.70(2H,m),1.30-1.05(4H,m)	DMSO $-d_6$	414	90	63
104		8.6(1H,s),8.0(1H,d),4.6(2H,s),4.2(1H,m),4.1(2H,t),3.9(1H,m),3.7(1H,m),3.1(1H,m),2.9-2.7(2H,m),2.8(1H,s),2.5(2H,t),1.2-1.0(4H,m)	DMSO $-d_6$	428	15	65
105		8.6(1H,s),8.0(1H,d),4.6(2H,s),4.2(1H,m),3.9(1H,m),3.7(1H,m),3.4(2H,s),3.3(3H,s),3.0(1H,m),2.8-2.6(2H,m),1.2-1.0(4H,m)	DMSO $-d_6$	420	20	52
106		8.6(1H,s),8.05(1H,d),4.6(2H,s),4.3(2H,t),4.2(1H,m),3.9(1H,m),3.8(2H,t),3.7(1H,m),3.1(1H,m),2.9-2.7(2H,m),1.2-1.0(4H,m)	DMSO $-d_6$	438	10	50

Table 17. Examples 107 to 116



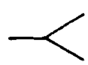
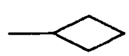
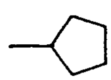
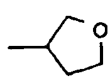
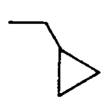
Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
107		8.8(1H,s),7.8(1H,d),4.7(1H,m),4.5(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),2.9(1H,m),2.8-2.7(2H,m),1.15(4H,s),0.9(6H,d)	DMSO $-d_6$	435	2	69
108		8.8(1H,s),7.8(1H,d),4.8(1H,m),4.4(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),2.9(1H,m),2.8-2.7(2H,m),2.2(2H,m),2.1(2H,m),1.7(1H,m),1.5(1H,m),1.15(4H,s)	DMSO $-d_6$	447	2	61
109		8.8(1H,s),7.8(1H,d),4.7(1H,m),4.5(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),2.9(1H,m),2.8-2.7(2H,m),1.7(4H,s),1.6(2H,m),1.5(2H,m),1.15(2H,m),1.0(2H,m)	DMSO $-d_6$	461	2	63
110		8.8(1H,s),7.8(1H,d),4.8(1H,m),4.5(2H,s),4.1(1H,m),3.9(1H,m),3.8-3.6(4H,m),3.1(1H,m),2.8-2.7(2H,m),2.3-1.9(2H,m),1.2-1.0(4H,s)	DMSO $-d_6$	463	2	54
111		8.8(1H,s),7.8(1H,d),4.5(2H,s),4.1(1H,m),3.9(1H,m),3.8(2H,dd),3.75(1H,m),3.1(1H,m),2.8-2.7(2H,m),1.15(4H,m),1.05(1H,m),0.5(2H,m),0.3(2H,m)	DMSO $-d_6$	447	2	59

Table 17. (continued)

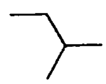
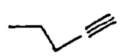
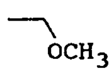
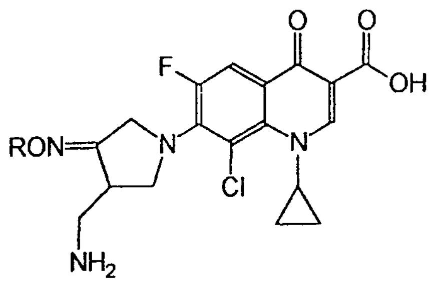
Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
112		8.8(1H,s),7.8(1H,d),4.5(2H,s),4.1(1H,m),3.9(1H,m),3.8(2H,d),3.75(1H,m),3.0(1H,m),2.8-2.7(2H,m),1.9(1H,m),1.2-1.0(4H,m),0.9(6H,d)	DMSO $-d_6$	449	2	64
113		8.8(1H,s),7.8(1H,d),4.62(2H,s),4.3(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),3.5(1H,s),2.9(1H,m),2.8-2.7(2H,m),1.15(4H,m)	DMSO $-d_6$	431	4	55
114		8.8(1H,s),7.8(1H,d),4.5(2H,s),4.1(1H,m),4.0(2H,t),3.9(1H,m),3.8(1H,m),3.1(1H,m),2.8-2.7(2H,m),2.7(1H,s),2.5(2H,t),1.2(4H,m)	DMSO $-d_6$	445	2	65
115		8.8(1H,s),7.8(1H,d),4.5(2H,s),4.1(1H,m),3.9(1H,m),3.8(1H,m),3.3(2H,s),3.1(3H,s),3.0(1H,m),2.8-2.7(2H,m),1.15(4H,m)	DMSO $-d_6$	437	1.5	47
116		8.8(1H,s),7.8(1H,d),4.5(2H,s),4.3(2H,t),4.1(1H,m),3.9(1H,m),3.8(2H,t),3.75(1H,m),3.0(1H,m),2.8-2.7(2H,m),1.15(4H,m)	DMSO $-d_6$	455	1.5	53

Table 18. Examples 117 to 126



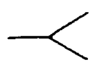
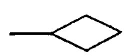
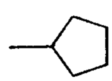
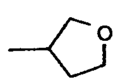
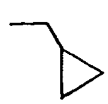
Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
117		8.8(1H,s),7.9(1H,d),4.7(1H,m),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.8-0.9(4H,m),0.9(6H,d)	DMSO $-d_6$	451	2.5	68
118		8.8(1H,s),7.9(1H,d),4.7(1H,m),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.2(2H,m),2.1(2H,m),1.7(1H,m),1.5(1H,m),1.12-0.9(4H,m)	DMSO $-d_6$	463	2	61
119		8.8(1H,s),7.9(1H,d),4.7(1H,m),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.7(4H,s),1.6(2H,m),1.5(2H,m),1.2-0.9(4H,m)	DMSO $-d_6$	477	2	55
120		8.8(1H,s),7.9(1H,d),4.8(1H,m),4.4(2H,s),4.3(1H,m),3.8-3.6(6H,m),3.0(1H,m),2.9-2.7(2H,m),2.3-1.9(2H,m),1.2-0.9(4H,m)	DMSO $-d_6$	479	2.5	49
121		8.8(1H,s),7.9(1H,d),4.4(2H,s),4.3(1H,m),3.8-3.7(4H,m),3.0(1H,m),2.9-2.7(2H,m),1.2-0.9(5H,m),0.5(2H,m),0.3(2H,m)	DMSO $-d_6$	463	2	52

Table 18. (continued)

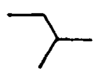
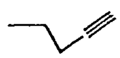
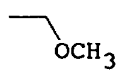
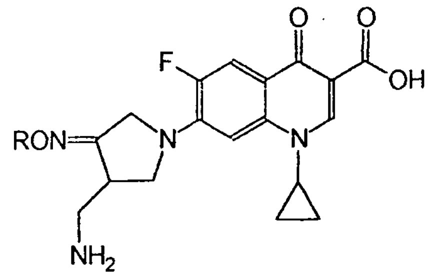
Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
122		8.8(1H,s),7.9(1H,d),4.4(2H,s),4.3(1H,m),3.8-3.7(4H,m),3.0(1H,m),2.9-2.7(2H,m),1.9(1H,m),1.2-0.9(4H,m),0.9(6H,d)	DMSO-d_6	465	2	60
123		8.8(1H,s),7.9(1H,d),4.61(2H,s),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.5(1H,s),3.0(1H,m),2.9-2.7(2H,m),1.2-0.9(4H,m)	DMSO-d_6	447	2	62
124		8.8(1H,s),7.9(1H,d),4.4(2H,s),4.3(1H,m),4.1(2H,t),3.8(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.8(1H,s),2.5(2H,t),1.2-0.9(4H,m)	DMSO-d_6	461	2.5	57
125		8.8(1H,s),7.9(1H,d),4.4(2H,s),4.3(1H,m),3.8(1H,m),3.7(1H,m),3.3(2H,s),3.1(3H,s),3.0(1H,m),2.9-2.7(2H,m),1.2-0.9(4H,m)	DMSO-d_6	453	1.5	51
126		8.8(1H,s),7.9(1H,d),4.4(2H,s),4.3(3H,m),3.8-3.7(4H,m),3.0(1H,m),2.9-2.7(2H,m),1.2-0.9(4H,m)	DMSO-d_6	471	2	64

Table 19. Examples 127 to 136



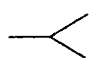
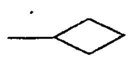
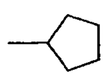
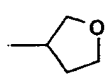
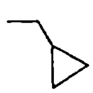
Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
127		8.6(1H,s),7.8(1H,d),7.2(1H,d),4.6(1H,m),4.4(2H,s),3.9(1H,m),3.8(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.3-1.1(4H,m),0.9(6H,d)	DMSO-d_6	417	3	55
128		8.6(1H,s),7.8(1H,d),7.2(1H,d),4.7(1H,m),4.4(2H,s),3.9(1H,m),3.8(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.2(2H,m),2.1(2H,m),1.7(1H,m),1.5(2H,m),1.3-1.1(4H,m)	DMSO-d_6	429	3	52
129		8.6(1H,s),7.8(1H,d),7.2(1H,d),4.7(1H,m),4.4(2H,s),3.9(1H,m),3.8(1H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.7(4H,s),1.6(2H,m),1.5(2H,m),1.3-1.1(4H,m)	DMSO-d_6	443	3	59
130		8.6(1H,s),7.8(1H,d),7.2(1H,d),4.8(1H,m),4.4(2H,s),3.9(1H,m),3.8-3.6(6H,m),3.0(1H,m),2.9-2.7(2H,m),2.3-1.9(2H,m),1.3-1.1(4H,m)	DMSO-d_6	445	3	45
131		8.6(1H,s),7.8(1H,d),7.2(1H,d),4.6(1H,m),4.4(2H,s),3.9(1H,m),3.8-3.7(3H,m),3.1(1H,m),2.9-2.7(2H,m),1.3-1.1(4H,m),1.0(1H,m),0.5(2H,m),0.3(2H,m)	DMSO-d_6	429	3	57

Table 19. (continued)

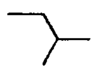
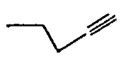
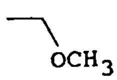
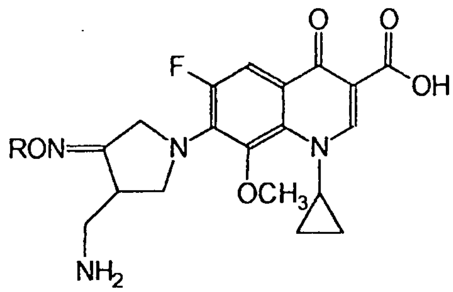
Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
132		8.6(1H,s),7.8(1H,d),7.2(1H,d),4.4(2H,s),3.9(1H,m),3.8(3H,m),3.7(1H,m),3.1(1H,m),2.9-2.7(2H,m),1.9(1H,m),1.3-1.1(4H,m),0.9(6H,d)	DMSO $-d_6$	431	3	76
133		8.6(1H,s),7.8(1H,d),7.2(1H,d),4.6(2H,s),4.4(2H,s),3.9(1H,m),3.8(1H,m),3.7(1H,m),3.5(1H,s),3.0(1H,m),2.9-2.7(2H,m),1.3-1.1(4H,m)	DMSO $-d_6$	413	3	49
134		8.6(1H,s),7.8(1H,d),7.2(1H,d),4.4(2H,s),4.1(2H,t),3.9(1H,m),3.8(1H,m),3.7(1H,m),3.1(1H,m),2.9-2.7(2H,m),2.8(1H,s),2.5(2H,t),1.3-1.1(4H,m)	DMSO $-d_6$	427	3	59
135		8.6(1H,s),7.8(1H,d),7.2(1H,d),4.4(2H,s),4.1(2H,t),3.9(1H,m),3.8(1H,m),3.7(1H,m),3.3(2H,s),3.2(3H,s),3.0(1H,m),2.9-2.7(2H,m),1.3-1.1(4H,m)	DMSO $-d_6$	419	1.5	47
136		8.6(1H,s),7.8(1H,d),7.2(1H,d),4.4(2H,s),4.3(2H,t),3.9(1H,m),3.8(3H,m),3.7(1H,m),3.0(1H,m),2.9-2.7(2H,m),1.3-1.1(4H,m)	DMSO $-d_6$	437	2	53

Table 20. Examples 137 to 146



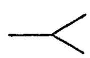
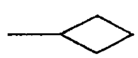
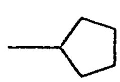
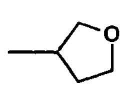
Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
137		8.8(1H,s),7.8(1H,d),4.7(1H,m),4.5(2H,s),4.3(1H,m),4.1(1H,m),3.9(1H,m),3.0(1H,m),2.8-2.7(2H,m),2.65(3H,s),1.3(2H,m),1.0(2H,m),0.9(6H,d)	DMSO $-d_6$	447	9	57
138		8.8(1H,s),7.8(1H,d),4.8(1H,m),4.7(2H,s),4.3(1H,m),4.2(1H,m),3.9(1H,m),3.0(1H,m),2.9-2.7(2H,m),2.7(3H,s),2.2(2H,m),2.1(2H,m),1.6(1H,m),1.5(1H,m),1.3(2H,m),0.95(2H,m)	DMSO $-d_6$	459	12	65
139		8.8(1H,s),7.8(1H,d),4.7(1H,m),4.5(2H,s),4.3(1H,m),4.2(1H,m),3.9(1H,m),3.1(1H,m),2.9-2.8(2H,m),2.7(3H,s),1.7(4H,s),1.6(2H,m),1.5(2H,m),1.3(2H,m),0.9(2H,m)	DMSO $-d_6$	473	12	63
140		8.8(1H,s),7.8(1H,d),4.8(1H,m),4.6(2H,s),4.3(1H,m),4.2(1H,m),4.0(1H,m),3.8-3.6(4H,m),3.1(1H,m),2.9-2.7(2H,m),2.7(3H,s),2.3-1.9(2H,m),1.3(2H,m),0.9(2H,m)	DMSO $-d_6$	475	12	42

Table 20. (continued)

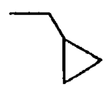
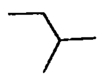
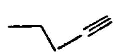
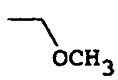
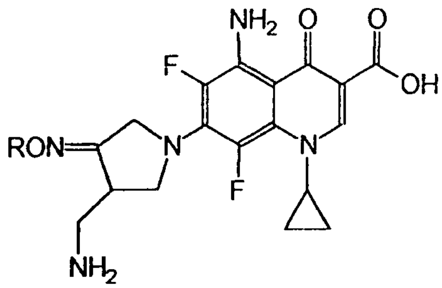
Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
141		8.8(1H,s),7.8(1H,d),4.6(2H,s),4.3(1H,m),3.9(1H,m),3.85(2H,dd),3.1(1H,m),3.0-2.8(2H,m),2.7(3H,s),1.3(2H,m),1.1(1H,m),0.9(2H,m),0.5(2H,m),0.3(2H,m)	DMSO $-d_6$	459	12	63
142		8.8(1H,s),7.8(1H,d),4.6(2H,s),4.3(1H,m),4.2(1H,m),3.95(1H,m),3.8(2H,d),3.05(1H,m),2.9-2.7(2H,m),2.7(3H,s),1.9(1H,m),1.3(2H,m),1.0(2H,m),0.9(6H,d)	DMSO $-d_6$	461	12	68
143		8.8(1H,s),7.8(1H,d),4.62(2H,s),4.60(2H,s),4.3(1H,m),4.1(1H,m),3.9(1H,m),3.5(1H,s),3.0(1H,m),2.7(3H,s),2.9-2.7(2H,m),1.3(2H,m),1.0(2H,m)	DMSO $-d_6$	443	12	30
144		8.8(1H,s),7.8(1H,d),4.6(2H,s),4.3(1H,m),4.2(1H,m),4.15(2H,t),3.1(1H,m),2.9-2.7(2H,m),2.8(1H,s),2.7(3H,s),2.5(3H,t),1.3(2H,m),0.9(2H,m)	DMSO $-d_6$	457	12	52
145		8.8(1H,s),7.8(1H,d),4.6(2H,s),4.3(1H,m),4.15(1H,m),3.9(1H,m),3.3(2H,s),3.1(3H,s),2.9(1H,m),2.8-2.6(2H,m),2.7(3H,s),1.3(2H,m),0.9(2H,m)	DMSO $-d_6$	449	8	39
146		8.8(1H,s),7.8(1H,d),4.6(2H,s),4.3(2H,t),4.25(1H,m),4.2(1H,m),3.9(1H,m),3.8(2H,t),2.9-2.7(2H,m),2.7(3H,s),1.3(2H,m),1.0(2H,m)	DMSO $-d_6$	467	12	57

Table 21. Examples 147 to 156



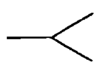
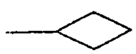
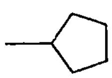
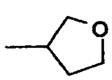
Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
147		8.4(1H,s),7.7(2H,br),4.5(1H,m),4.3(2H,s),4.0-3.8(3H,m),3.2(1H,m),2.8-2.6(2H,m),1.1(4H,s),0.9(6H,d)	DMSO $-d_6$	450	5	73
148		8.3(1H,s),7.3(2H,br),4.8(1H,m),4.3(2H,s),4.0-3.8(3H,m),2.8-2.6(2H,m),2.2(2H,m),2.1(2H,m),1.6(1H,m),1.5(1H,m),1.1(4H,m)	DMSO $-d_6$	462	8	64
149		8.4(1H,s),7.4(2H,br),4.7(1H,m),4.5(2H,s),4.2(1H,m),3.9(1H,m),3.7(1H,m),3.0(1H,m),2.8-2.6(2H,m),1.7(4H,s),1.6(2H,m),1.5(2H,m),1.1(4H,m)	DMSO $-d_6$	476	8	61
150		8.4(1H,s),7.4(2H,br),4.8(1H,m),4.6(2H,s),4.2(1H,m),4.0(1H,m),3.8-3.6(4H,m),3.0(1H,m),2.8-2.6(2H,m),2.3-1.9(2H,m),1.2-0.9(4H,m)	DMSO $-d_6$	478	12	54

Table 21. (continued)

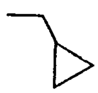
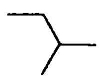
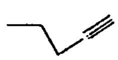
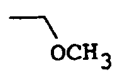
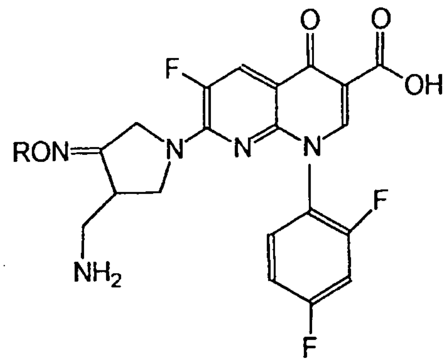
Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
151		8.4(1H,s),7.5(2H,br),4.6(2H,s),3.9(1H,m),3.8(2H,dd),3.0(1H,m),2.9-2.8(2H,m),1.0(1H,m),0.5(2H,m),0.3(2H,m)	DMSO-d_6	462	5	82
152		8.4(1H,s),7.5(2H,br),4.5(2H,s),3.9(1H,m),3.8(2H,dd),3.1(1H,m),2.9-2.7(2H,m),1.9(1H,m),1.2-1.1(4H,m),0.9(6H,d)	DMSO-d_6	464	6	75
153		8.4(1H,s),7.4(2H,br),4.6(2H,s),4.59(2H,m),4.2(1H,m),3.9(1H,m),3.7(1H,m),3.5(1H,s),3.0(1H,m),2.8-2.6(2H,m),1.1(4H,s)	DMSO-d_6	446	4	50
154		8.4(1H,s),7.5(2H,br),4.4(2H,s),4.1(1H,m),4.0(2H,t),3.9(1H,m),3.8(1H,m),3.1(1H,m),2.8-2.7(2H,m),2.8(1H,s),2.5(2H,t),1.2-0.9(4H,m)	DMSO-d_6	460	5	70
155		8.4(1H,s),7.4(2H,br),4.4(2H,s),4.3(2H,t),4.1(1H,m),3.9(1H,m),3.7(2H,t),3.6(1H,m),3.3(2H,s),3.0(3H,s),2.9(1H,m),2.8-2.6(2H,m),1.3-0.9(4H,m)	DMSO-d_6	452	3	60
156		8.4(1H,s),7.4(2H,br),4.4(2H,s),4.3(2H,t),4.0(2H,m),3.9(1H,m),3.8(2H,t),3.7(1H,m),3.2(1H,m),2.9-2.7(2H,m),1.1(4H,s)	DMSO-d_6	470	5	72

Table 22. Examples 157 to 166



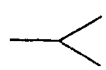
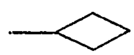
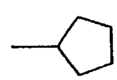
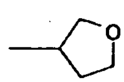
Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (min)	Yield (%)
157		8.8(1H,s),8.1(1H,d),7.8(1H, m),7.6(1H,dd),7.3(1H,dd), 4.6(1H,m),4.3(2H,s),4.0(1H, m),3.9(1H,m),3.0(1H,m), 2.8-2.6(2H,m),0.9(6H,d)	DMSO $-d_6$	490	15	64
158		8.8(1H,s),8.1(1H,d),7.8(1H, m),7.6(1H,dd),7.3(1H,dd), 4.7(1H,m),4.4(2H,s),4.0(1H, m),3.9(1H,m),3.0(1H,m),2.8-2.6(2H,m),2.2(2H,m),2.1(2H, m),1.7(1H,m),1.5(1H,m)	DMSO $-d_6$	502	20	61
159		8.8(1H,s),8.1(1H,d),7.8(1H, m),7.6(1H,dd),7.3(1H,dd), 4.7(1H,m),4.4(2H,s),4.0(1H, m),3.9(1H,m),3.0(1H,m),2.8-2.6(2H,m),2.2(2H,m),2.1(2H, m),1.7(1H,m),1.5(1H,m)	DMSO $-d_6$	516	35	70
160		8.8(1H,s),8.1(1H,d),7.8(1H, m),7.6(1H,dd),7.3(1H,dd), 4.8(1H,m),4.4(2H,s),4.0(1H, m),3.9(1H,m),3.8-3.6(4H, m),3.0(1H,m),2.9-2.6(2H, m),2.3-1.9(2H,m)	DMSO $-d_6$	518	35	55

Table 22. (continued)

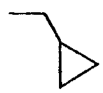
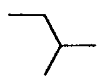
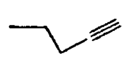
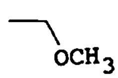
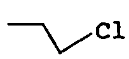
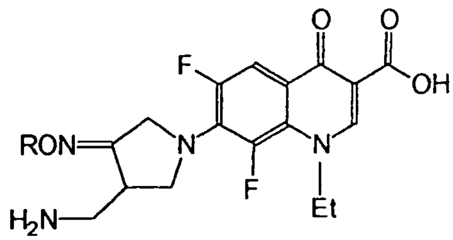
Examp. No.	R	^{1}H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (min)	Yield (%)
161		8.8(1H,s),8.1(1H,d),7.8(1H,dd),7.6(1H,dd),7.3(1H,dd),4.6(2H,s),4.2(1H,m),3.9(1H,m),3.8(2H,dd),3.0(1H,m),2.8-2.6(2H,m),1.1(1H,m),0.5(2H,m),0.3(2H,m)	DMSO -d_6	502	30	65
162		8.8(1H,s),8.1(1H,d),7.8(1H,dd),7.6(1H,dd),7.3(1H,dd),4.6(2H,s),4.0(1H,m),3.9(1H,m),3.8(2H,d),3.0(1H,m),2.8-2.6(2H,m),1.9(1H,m),0.9(6H,d)	DMSO -d_6	504	20	70
163		8.79(1H,s),8.01(1H,d),7.8(1H,m),7.6(1H,dd),7.3(1H,dd),4.73(2H,s),4.61(2H,s),4.21(1H,m),3.75(1H,m),3.50(1H,s),3.35(2H,s),3.08(1H,m),2.90-2.70(2H,m)	DMSO -d_6	486	60	52
164		8.8(1H,s),8.1(1H,d),7.8(1H,m),7.6(1H,dd),7.3(1H,dd),4.6(2H,s),4.1(1H,m),4.0(2H,t),3.9(1H,m),3.0(1H,m),2.8-2.6(2H,m),2.7(1H,s),2.5(2H,t)	DMSO -d_6	500	25	53
165		8.8(1H,s),8.1(1H,d),7.8(1H,m),7.6(1H,dd),7.3(1H,dd),4.6(2H,s),4.1(1H,m),3.9(1H,m),3.3(2H,s),3.1(3H,s),3.0(1H,m),2.8-2.6(2H,m)	DMSO -d_6	492	30	47
166		8.8(1H,s),8.1(1H,d),7.8(1H,m),7.6(1H,dd),7.3(1H,m),4.6(2H,s),4.3(2H,t),4.1(1H,m),3.9(1H,m),3.8(2H,t),3.1(1H,m),2.8-2.6(2H,m)	DMSO -d_6	510	15	51

Table 23. Examples 167 to 176



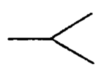
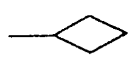
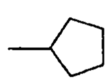
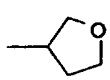
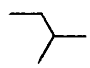
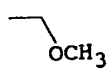
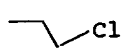
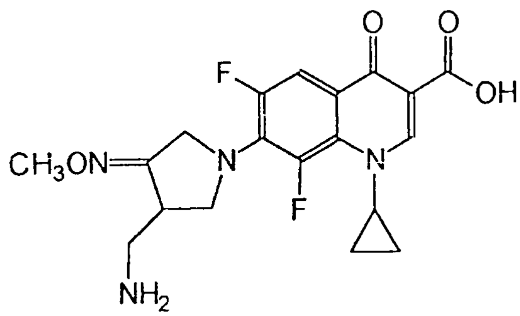
Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
167		8.8(1H,s),7.8(1H,d),4.6(1H,m),4.5(2H,q),4.4(2H,s),4.2(1H,m),3.9(1H,m),3.1(1H,m),2.9-2.7(2H,m),1.45(3H,t),0.9(6H,d)	DMSO $-d_6$	423	4.5	82
168		8.8(1H,s),7.8(1H,d),4.7(1H,m),4.5(2H,q),4.4(2H,s),4.2(1H,m),4.1(1H,m),3.1(1H,m),2.9-2.7(2H,m),2.2(2H,m),2.1(2H,m),1.7(1H,m),1.6(1H,m),1.45(3H,t)	DMSO $-d_6$	435	5	73
169		8.8(1H,s),7.8(1H,d),4.75(1H,m),4.6(2H,s),4.5(2H,q),4.2(1H,m),3.9(1H,m),3.0-2.7(2H,m),1.8(4H,s),1.65(2H,s),1.5(2H,s),1.4(3H,t)	DMSO $-d_6$	449	5	77
170		8.7(1H,s),7.8(1H,d),4.8(1H,m),4.55(2H,s),4.5(2H,dd),4.15(1H,m),3.85(1H,m),3.7(2H,m),3.1(1H,m),2.9-2.7(2H,m),2.1-1.9(2H,m),1.5(3H,t)	DMSO $-d_6$	451	6	71

Table 23. (continued)

Examp. No.	R	^1H NMR, δ(ppm)	NMR solv.	FAB, MS (M+1)	Reac. time (hr)	Yield (%)
171		8.8(1H,s),7.8(1H,d),4.6 (2H,s),4.45(2H,m),4.25(1H, m),3.9(2H,dd),3.7(1H,m), 3.1(1H,m),1.45(3H,t),0.5 (2H,m),0.25(2H,m)	DMSO $-d_6$	435	5	84
172		8.8(1H,s),7.8(1H,d),4.6(2H, s),4.5(2H,q),4.2(1H,m),3.9 (1H,m),3.85(2H,dd),3.1(1H, m),2.9-2.7(2H,m),1.9(1H,m), 0.9(6H,d)	DMSO $-d_6$	437	4	70
173		8.8(1H,s),7.8(1H,d),4.62 (2H,s),4.5(2H,q),4.4(2H,s), 4.2(1H,m),3.9(1H,m),3.5(1H, s),3.1(1H,m),2.9-2.7(2H,m), 1.45(3H,t)	DMSO $-d_6$	419	3	50
174		8.8(1H,s),7.8(1H,d),4.5(2H, dd),4.2(1H,m),4.15(2H,t), 3.9(1H,m),3.1(1H,m),2.9-2.7(2H,m),2.8(1H,s),2.5(2H, t),1.5(3H,t)	DMSO $-d_6$	433	4.5	72
175		8.8(1H,s),7.8(1H,d),4.6(2H, s),4.5(2H,dd),4.15(1H,m), 3.9(1H,m),3.3(2H,s),3.1(3H, s),2.9(1H,m),2.8(1H,m),2.6 (1H,m),1.5(3H,t)	DMSO $-d_6$	425	2	39
176		8.8(1H,s),7.8(1H,d),4.6(2H, s),4.5(2H,dd),4.3(2H,t),4.2 (1H,m),3.9(1H,m),3.8(2H,t), 2.9-2.7(2H,m),1.5(3H,t)	DMSO -d6	443	2	57

Example 177

Synthesis of 7-(4-amino-3-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



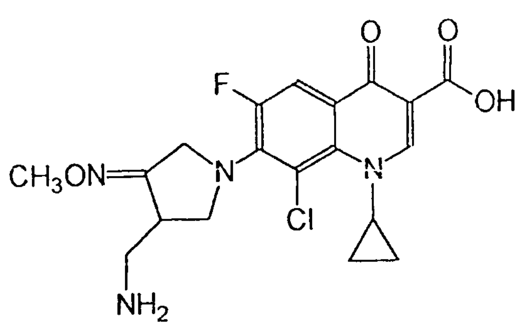
2.83g (10 mmole) of 1-cyclopropyl-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 4.27g (11.5 mmole) of 4-aminomethyl-pyrrolidin-3-one O-methyloxime ditrifluoroacetate were added to 23ml of dry acetonitrile. Then, 4.6g (30 mmole) of 1,8-diazabicyclo[5.4.0]undec-7-ene was added thereto and the mixture was refluxed for 1.5 hours under heating and then cooled down to room temperature. 15ml of distilled water was added to the reaction solution. The precipitated solid product was separated and dried to obtain 2.24g (Yield: 55%) of the title compound.

^{1}H NMR (DMSO-d$_6$, ppm) : δ 8.6(1H, s), 7.75(1H, d), 4.35(2H, s), 4.1-3.9(2H, m), 3.8(3H, s), 3.7(1H, m), 3.35(1H, m), 2.9-2.6(2H, m), 1.25 (2H, d), 0.95(2H, s)

FAB MS (POS) : [M+H] = 407

Example 178

Synthesis of 7-(4-aminomethyl-3-methoxyiminopyrrolidin-1-yl)-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic aicd



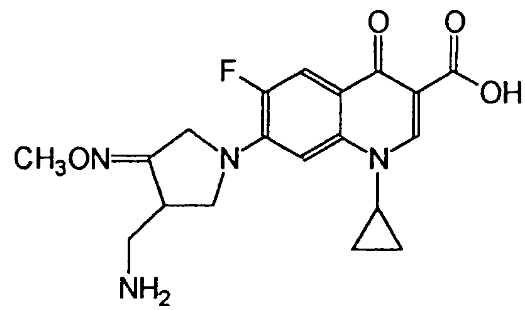
141mg (0.5 mmole) of 1-cyclopropyl-8-chloro-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 205mg (0.55 mmole) of 4-aminomethylpyrrolidin-3-one O-methyloxime ditrifluoroacetate were reacted for one hour according to the same manner as Example 177. Then, the reaction solution was concentrated and the residue was purified with preparative HPLC to obtain 88mg (Yield: 42%) of the title compound.

^{1}H NMR (DMSO-d$_6$, ppm) : δ 8.7(1H, s), 7.85(1H, d), 4.4(1H, m), 3.75(3H, s), 3.7(3H, m), 3.4(2H, m), 3.0-2.7(2H, m), 1.25(2H, d), 1.0(2H, s)

FAB MS(POS) : [M+H] = 423

Example 179

Synthesis of 7-(4-aminomethyl-3-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



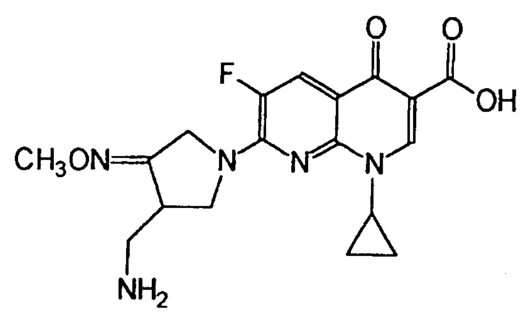
132mg (0.5 mmole) of 1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 205mg (0.55 mmole) of 4-aminomethylpyrrolidin-3-one O-methyloxime ditrifluoroacetate were reacted for 3 hours according to the same manner as Example 177. Then, the reaction solution was concentrated and the residue was purified with preparative HPLC to obtain 73mg (Yield: 37%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) : δ 8.6(1H, s), 7.85(1H, d), 7.2(1H, d), 4.4(2H, d), 3.9(1H, m), 3.85(3H, s), 3.8-3.65(2H, m), 3.0(1H, m), 2.9-2.7(2H, m), 1.3(2H, m), 1.1(2H, m)

FAB MS(POS) : [M+H] = 389

Example 180

Synthesis of 7-(4-aminomethyl-3-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]-naphthyridine-3-carboxyic acid



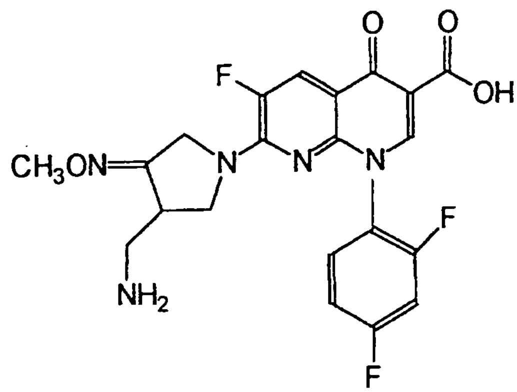
141mg (0.5 mmole) of 1-cyclopropyl-7-chloro-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid and 205mg (0.5 mmole) of 4-aminomethylpyrrolidin-3-one O-methyloxime ditrifluoroacetate were reacted for 0.5 hour according to the same manner as Example 177 to obtain 167mg (Yield: 85%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) : δ 8.6(1H, s), 8.05(1H, d), 4.55(2H, s), 4.3(1H, m), 3.85(3H, s, 1H, m), 3.7 (1H, m), 3.1-3.0(2H, m), 1.2-1.0(4H, m)

FAB MS(POS) : [M+H] = 390

Example 181

Synthesis of 7-(4-aminomethyl-3-methoxyiminopyrrolidin-1-yl)-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid

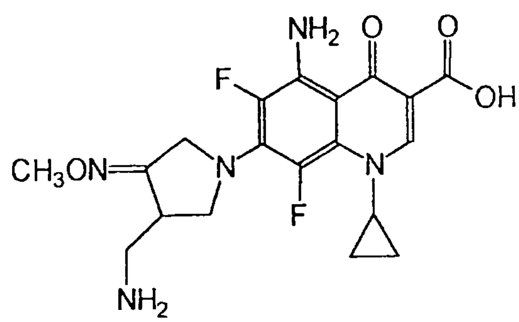


177mg (0.5 mmole) of 1-(2,4-difluorophenyl)-7-chloro-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid and 205mg (0.55 mmole) of 4-aminomethylpyrrolidin-3-one O-methyloxime ditrifluoroacetate were reacted for 0.5 hour according to the same manner as Example 177 to obtain 59mg (Yield: 25%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) :	δ 8.85(1H, s), 8.05(1H, d), 7.75(1H, dd), 7.6(1H, dd), 7.35(1H, dd), 4.3(2H, m), 3.8(3H, s, 1H, m), 3.6(1H, m), 3.0 (1H, m), 2.7(2H, m)
FAB MS(POS) :	[M+H] = 462

Example 182

Synthesis of 1-cyclopropyl-5-amino-6,8-difluoro-7-(4-aminomethyl-3-methyloxyiminopyrrolidin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



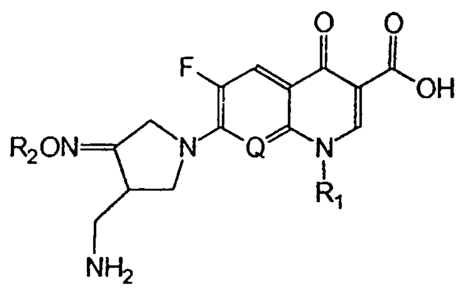
148mg (0.5 mmole) of 1-cyclopropyl-5-amino-6,7,8-trifluoro-4 -oxo-1,4-dihydroquinoline-3-carboxylic acid and 205mg (0.55 mmole) of 4-aminomethylpyrrolidin-3-one O-methyloxime ditrifluoroacetate were refluxed for 4 hours under heating according to the same manner as Example 177. Then, the reaction solution was concentrated and the residue was purified with preparative HPLC to obtain 84mg (Yield: 40%) of the title compound.

^{1}H NMR (DMSO-d_6, ppm) :	δ 8.49(1H, s), 7.28(2H, bs), 4.3(2H, s), 3.9(2H, m), 3.8(3H, s), 3.7(1H, m), 2.6-2.8(3H, m), 1.05(4H, m)
FAB MS(POS) :	$[M+H]^+$ = 422

Examples 183 to 202

The compounds prepared in Preparations 40 and 55 to 57 were treated according to the same procedure as Example 177 to 182 to prepare the respective compounds 183 to 202 of which NMR and MS data are listed in the following Table 24.

Table 24. Examples 183 to 202



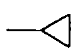
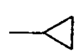
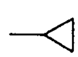
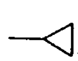
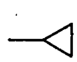
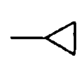
Ex. No.	Q	R_1	R_2	^1H NMR(DMSO-d_6) δ(ppm)	FAB MS (POS) [M+H]	Reac. Time (hr)	Yield (%)
183	CF		H	8.8(1H,s),7.9(1H,d),4.35(1H,m),3.8(2H,m),3.7(2H,m),3.4(1H,m),3.0(2H,m),1.2-1.0(4H,m)	393	2.5	41
184	CF		Et	8.8(1H,s),7.9(1H,d),4.4(1H,m),4.2(2H,q),4.1-3.9(2H,m),3.4(2H,m),2.8(2H,m),1.4(3H,t),1.25-1.0(4H,m)	421	2	38
185	CF		Ph	8.8(1H,s),7.9(1H,d),7.3-7.1(5H,m),4.3(1H,m),3.9-3.7(3H,m),3.4(2H,m),2.8(2H,m),1.2(2H,d),1.05(2H,s)	469	4	29
186	CF		tBu	8.8(1H,s),7.9(1H,d),4.35(1H,d),4.1-3.9(3H,m),3.4(2H,m),2.9-2.7(2H,m),1.35(9H,s),1.2-0.95(4H,m)	449	2	35
187	CCl		H	8.9(1H,s),7.9(1H,d),4.4(1H,m),3.8(2H,m),3.7(2H,m),3.4(1H,m),2.9(2H,m),1.25(2H,m),1.1(2H,s)	409	1.5	39
188	CCl		Et	8.9(1H,s),7.9(1H,d),4.35(1H,m),4.2(2H,q),3.95-3.75(3H,m),3.7(2H,m),3.4(2H,m),2.85-2.7(2H,m),1.4(3H,t),1.3-1.15(4H,m)	437	1.5	37

Table 24. (continued)

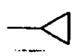
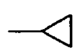
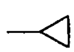
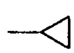
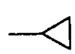
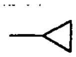
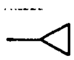
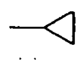
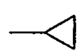
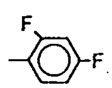
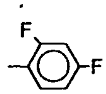
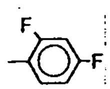
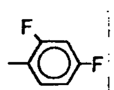
Ex. No.	Q	R_1	R_2	^1H NMR(DMSO-d_6) δ(ppm)	FAB MS (POS) [M+H]	Reac. Time (hr)	Yield (%)
189	CCl		Ph	8.9(1H,s),7.9(1H,d),7.3-7.1 (5H,m),4.35(1H,m),4.1-3.9 (3H,m),3.65(2H,m),3.35(2H, m),2.8-2.7(2H,m),1.15(2H,d), 0.95(2H,s)	485	4.5	25
190	CCl		tBu	8.9(1H,s),7.85(1H,d),4.3(1H, m),3.95-3.8(3H,m),3.7(2H,m), 3.4(2H,m),2.8(2H,m),1.3(9H, s),1.2-1.0(4H,m)	465	3	51
191	CH		H	8.6(1H,s),7.85(1H,d),7.2(1H, d),4.4(1H,m),3.9(2H,m),3.8-3.65(3H,m),2.9-2.7(2H,m),1.3 (2H,d),1.1(2H,s)	375	2.2	42
192	CH		Et	8.6(1H,s),7.8(1H,d),7.2(1H, d),4.4(1H,m),4.25(2H,q),3.9-3.7(3H,m),3.5(2H,m),2.9-2.7 (2H,m),1.3(3H,t),1.25-0.95 (4H,m)	403	1.5	40
193	CH		Ph	8.6(1H,s),7.8(1H,d),7.5-7.2 (5H,m,1H,d),4.35(1H,m),4.0-3.8(3H,m),3.5(2H,m),2.85-2.7 (2H,m),1.3(2H,d),1.15(2H,s)	451	4.5	31
194	CH		tBu	8.6(1H,s),7.75(1H,d),7.2(1H, d),4.35(1H,m),4.0-3.8(3H,m), 3.5(2H,m),2.9-2.7(2H,m),1.4 (9H,s),1.2-1.05(4H,m)	431	3	43
195	N		H	8.6(1H,s),8.1(1H,d),4.5(2H, s),4.3(1H,m),3.8(1H,m),3.65 (1H,m),3.35(1H,m),3.0-2.9 (2H,m),1.2-1.0(4H,m)	376	1	61
196	N		Et	8.6(1H,s),8.05(1H,d),4.55 (2H,s),4.3(1H,m),4.25(2H, q),3.8(1H,m),3.7(1H,m),3.4 (1H,m),3.0-2.85(2H,m),1.35 (3H,t),1.2-0.95(4H,m)	404	1	57

Table 24. (continued)

Ex. No.	Q	R_1	R_2	^1H NMR(DMSO-d_6) δ(ppm)	FAB MS (POS) [M+H]	Reac. Time (hr)	Yield (%)
197	N		Ph	8.6(1H,s),8.1(1H,d),7.7-7.3 (5H,m),4.6(2H,s),4.35(1H,m), 3.9(1H,m),3.75(1H,m),3.4(1H, m),3.05-2.8(3H,m),1.25(2H, d),1.05(2H,s)	452	1	40
198	N		tBu	8.6(1H,s),8.05(1H,d),4.55 (2H,s),4.35(1H,m),3.95(1H, m),3.7(1H,m),3.35(1H,m),3.0-2.85(2H,m),1.35(9H,s),1.15 (2H,d),1.0(2H,s)	432	1.5	54
199	N		H	8.85(1H,s),8.1(1H,d),7.75 (1H,m),7.6(1H,dd),7.35(1H, dd),4.3(1H,m),3.8(3H,m),3.6 (1H,m),3.0(1H,m),2.7(2H,m)	448	1	33
200	N		Et	8.85(1H,s),8.05(1H,d),7.75 (1H,m),7.6(1H,dd),7.35(1H, dd),4.3(1H,m),4.25(2H,q), 3.75(3H,m),3.6(2H,m),2.95 (2H,m),2.7-2.6(2H,m),1.4 (3H,t)	476	1	37
201	N		Ph	8.85(1H,s),8.1(1H,d),7.75 (1H,m),7.6(1H,dd),7.55-7.35 (5H,m,1H,dd),4.35(1H,m),3.75 (3H,m),3.65(2H,m),3.0(2H,m), 2.85(2H,m)	524	1.5	29
202	N		tBu	8.85(1H,s),8.05(1H,d),7.75 (1H,m),7.55(1H,dd),7.3(1H, dd),4.3(1H,m),3.8(3H,m),3.55 (2H,m),2.9(2H,m),2.7-2.65 (2H,m),1.3(9H,s)	504	0.5	41

Biological Example 1

In vitro antibacterial activity test

The antibacterial activity of the compounds according to the present invention was determined by measuring their minimum inhibitory concentrations (MIC, μg/ml) against standard strains, clinically isolated strains and strains resistant to some antibacterial agents. In this test, the known antibacterial compounds, ofloxacin and ciprofloxacin, were used as the comparative agents. The minimum inhibitory concentration could be determined by diluting the test compounds according to a two-times dilution method, dispersing the diluted test compounds in Mueller-Hinton agar medium and then inoculating 5μl of the standard strain

having 10^7 CFU per ml to the medium, which is then incubated for 18 hours at 37°C. The measured results are described in the following Table 25.

Table 25. Minimum Inhibitory Concentration of the test compounds (μg/ml)

Test Strains \ Examples	1	12	34	56	89
Staphylococcus aureus 6538p	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008
Staphylococcus aureus giorgio	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008
Staphylococcus aureus 77	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008
Staphylococcus aureus 241	2	1	4	2	1
Staphylococcus epidermidis 887E	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008
Staphylococcus epidermidis 178	2	0.5	2	2	0.5
Streptococcus faecalis 29212	0.031	0.031	0.13	0.016	0.063
Bacillus subtilis 6633	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008
Micrococcus luteus 9341	0.063	0.13	0.13	0.063	0.25
Escherichia coli 10536	≤0.008	≤0.008	0.016	≤0.008	0.016
Escherichia coli 3190Y	≤0.008	0.016	≤0.008	≤0.008	0.016
Escherichia coli 851E	0.016	0.063	0.13	≤0.008	0.063
Escherichia coli TEM3 3455E	0.25	0.5	1	0.5	0.25
Escherichia coli TEM5 3739E	0.063	0.25	0.5	0.25	0.13
Escherichia coli TEM9 2639E	0.063	0.25	0.13	0.063	0.063
Pseudomonas aeruginosa 1912E	1	2	0.5	2	2
Pseudomonas aeruginosa 10145	2	0.5	2	2	2
Acinetobacter calcoaceticus 15473	≤0.008	0.016	0.031	≤0.008	0.031
Citrobacter diversus 2046E	0.063	0.13	0.25	0.016	0.13
Enterobacter cloacae 1194E	0.031	0.13	0.25	0.031	0.13
Enterobacter cloacae P99	≤0.008	0.063	0.063	≤0.008	0.016
Klebsiella aerogenes 1976E	0.25	1	0.5	0.5	0.5
Klebsiella aerogenes 1082E	0.063	0.13	0.031	0.016	0.25
Salmonella typimurium 14028	0.13	0.25	0.063	0.031	0.13

Table 25. (continued)

Test Strains \ Examples	97	102	103	104	177
Staphylococcus aureus 6538p	≤0.008	0.016	≤0.008	≤0.008	≤0.008
Staphylococcus aureus giorgio	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008
Staphylococcus aureus 77	0.016	0.016	≤0.008	≤0.008	0.016
Staphylococcus aureus 241	2	4	4	8	0.5
Staphylococcus epidermidis 887E	≤0.008	≤0.008	≤0.008	0.016	≤0.008
Staphylococcus epidermidis 178	1	1	4	4	1
Streptococcus faecalis 29212	0.063	0.063	0.031	0.031	0.031
Bacillus subtilis 6633	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008
Micrococcus luteus 9341	0.063	0.063	0.13	0.13	0.063
Escherichia coli 10536	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008
Escherichia coli 3190Y	≤0.008	≤0.008	≤0.008	≤0.008	≤0.008
Escherichia coli 851E	0.031	0.063	≤0.008	≤0.008	0.031
Escherichia coli TEM3 3455E	0.13	0.5	0.13	0.25	0.25
Escherichia coli TEM5 3739E	0.063	0.25	0.063	0.13	0.13
Escherichia coli TEM9 2639E	0.031	0.063	0.031	0.031	0.063
Pseudomonas aeruginosa 1912E	1	2	0.5	1	0.5
Pseudomonas aeruginosa 10145	1	2	0.5	1	0.5
Acinetobacter calcoaceticus 15473	0.016	0.063	0.031	≤0.008	0.13
Citrobacter diversus 2046E	0.063	0.13	0.13	≤0.008	0.031
Enterobacter cloacae 1194E	0.063	0.25	0.016	≤0.008	0.063
Enterobacter cloacae P99	≤0.008	0.031	≤0.008	0.016	0.016
Klebsiella aerogenes 1976E	0.25	0.5	0.063	0.13	0.13
Klebsiella aerogenes 1082E	0.13	0.25	0.031	0.031	0.063
Salmonella typimurium 14028	0.13	0.25	0.031	0.031	0.063

Table 25. (continued)

Examples / Test Strains	178	179	180	OFLX	CFLX
Staphylococcus aureus 6538p	0.031	≤0.008	≤0.008	0.25	0.13
Staphylococcus aureus giorgio	0.016	0.016	≤0.008	0.25	0.25
Staphylococcus aureus 77	0.031	0.031	≤0.008	0.25	0.25
Staphylococcus aureus 241	1	2	2	64	64
Staphylococcus epidermidis 887E	0.031	0.016	≤0.008	0.25	0.13
Staphylococcus epidermidis 178	1	2	2	32	128
Streptococcus faecalis 29212	0.063	0.031	0.063	2	0.5
Bacillus subtilis 6633	0.016	≤0.008	≤0.008	0.063	0.031
Micrococcus luteus 9341	0.25	0.13	0.13	2	2
Escherichia coli 10536	0.031	≤0.008	≤0.008	0.031	≤0.008
Escherichia coli 3190Y	0.016	≤0.008	≤0.008	0.016	≤0.008
Escherichia coli 851E	0.063	≤0.008	≤0.008	0.063	0.016
Escherichia coli TEM3 3455E	1	0.13	0.25	0.5	0.25
Escherichia coli TEM5 3739E	0.5	0.063	0.13	0.5	0.13
Escherichia coli TEM9 2639E	0.25	0.031	0.031	0.063	0.031
Pseudomonas aeruginosa 1912E	0.5	0.25	0.25	0.5	0.31
Pseudomonas aeruginosa 10145	1	0.25	0.25	2	0.25
Acinetobacter calcoaceticus 15473	0.13	0.016	0.063	0.25	0.25
Citrobacter diversus 2046E	0.13	0.031	0.016	0.063	0.016
Enterobacter cloacae 1194E	0.13	0.031	0.031	0.063	0.031
Enterobacter cloacae P99	0.063	0.008	≤0.008	≤0.008	≤0.008
Klebsiella aerogenes 1976E	0.5	0.13	0.13	0.25	0.13
Klebsiella aerogenes 1082E	0.25	0.031	0.016	0.063	≤0.008
Salmonella typimurium 14028	0.063	0.063	0.031	0.13	0.031

Note) OFLX = Ofloxacin
CFLX = Ciprofloxacin

Biological Example 2

Pharmacokinetic test

The pharmacokinteic property parameters of the compounds of the present invention were determined using SD rats (male) weighing about 230±10g. Specifically, the test compounds of the present invention were administered in an amount of 20mg/kg of body weight to test rats via femoral veins. Then, bloods were collected at certain intervals after administration of the test compounds from femoral veins and analyzed by means of Agar Well Method to measure the blood concentration of the test compounds from which pharmacokinetic parameters, half life ($T_{1/2}$) and AUC (area under the curve) were calculated. The obtained results are described in the following Table 26.

Table 26. Pharmacokinetic parameters

	Route	$T_{1/2}$ (hr)	C_{max} (μg/ml)	T_{max} (hr)	F (%)
CFLX	IV	1.76±0.035			71
	PO	1.7 ±0.108	1.34±0.368	1.13±0.605	
EX.89	IV	2.29±1.13			>100
	PO	6.69±2.78	4.89±2.23	2.18±0.77	
EX.177	IV	1.92±0.38			47.23
	PO	3.93±1.31	0.37±0.11	0.51±0.33	

Note: CFLX = Ciprofloxacin
IV = Intravenous
PO = Per oral
$T_{1/2}$ = Biological half life

C_{max} = Maximum blood concentration
T_{max} = Time showing maximum blood concnetration after administration of the test compound
F = Bioavailability

Biological Example 3

Acute oral toxicity test

To determine the acute oral toxicity of the compounds prepared in Examples 1 and 34, the test solution containing the compounds in various concentrations were orally administered to ICR male mouse in an amount of 10ml per kg of body weight. For 7 days after administration, the lethality and the conditions of test mouse were observed, from which LD_{50} value (mg/kg) was calculated. The obtained results are described in the following Table 27.

Table 27

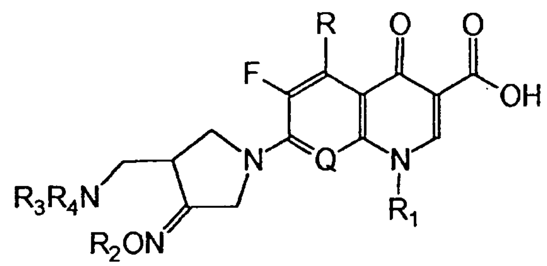
Toxicity	
Test Compound (Example No.)	LD_{50} value (mg/kg)
1	> 3,000
34	> 3,000

Although this invention has been described in its preferred form with a certain degree of particularity, it is appreciated by those skilled in the art that the present disclosure of the preferred form has been made

only by way of example and that numerous changes in the details of the construction, combination and arrangement of parts may be resorted to without departing from the spirit and scope of the invention.

Claims

1. A quinoline(naphthyridine) carboxylic acid derivative represented by the following formula (I) :



(I)

and its pharmaceutically acceptable non-toxic salt, its physiologically hydrolyzable ester, solvate and isomer, in which

R represents hydrogen, methyl or amino;

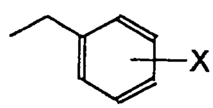
Q represents C-H, C-F, C-Cl, C-OH, $C-CH_3$, $C-O-CH_3$ or N;

R_1 represents cyclopropyl, ethyl, or phenyl which is substituted with one or more fluorine atom(s);

R_2 represents one of the following a) through e):

a) hydrogen, straight or branched C_1-C_4 alkyl, cyclopropyl, cyclopropylmethyl, C_3-C_6 alkynyl, 2-haloethyl, methoxymethyl, methoxycarbonylmethyl, aryl or allyl,

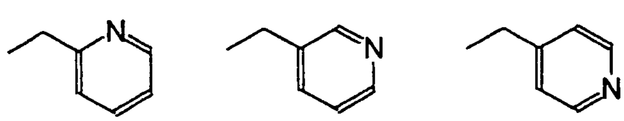
b) a group of the following formula (1),



(1)

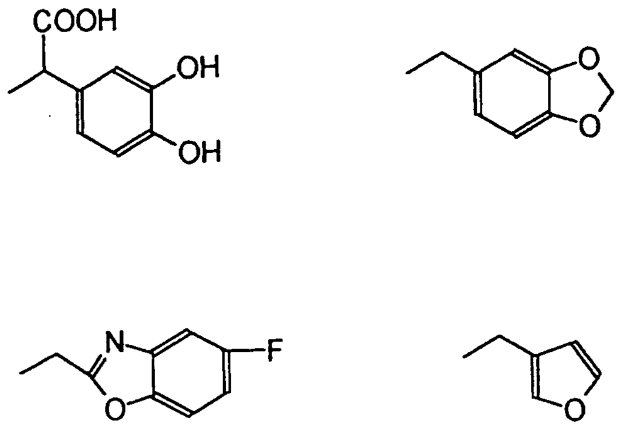
wherein X represents hydrogen, 2, 3 or 4-fluoro, cyano, nitro, methoxy, C_1-C_4 alkyl, or 2,4-difluoro,

c) a group of the following formula (2),



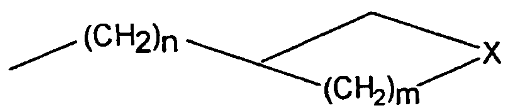
(2)

d) a heteroarylmethyl of the following formula (3),



(3)

e) a group of the following formula (4),



(4)

wherein n denotes 0 or 1, m denotes 0, 1 or 2 and X represents methylene, O or N, and

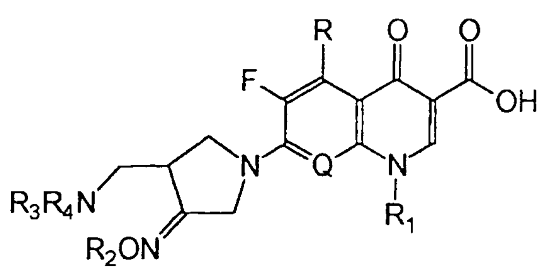
R_3 and R_4 independently of one another represent hydrogen or C_1-C_3 alkyl or R_3 and R_4 together with a nitrogen atom to which they are attached can form a ring.

2. The compound of claim 1, wherein Q represents C-H, C-F, C-Cl, C-OMe or N, R represents hydrogen or amino, R_1 represents cyclopropyl or 2,4-difluorophenyl, and R_2 represents hydrogen, methyl, isopropyl, t-butyl, phenyl, homopropargyl, 2-fluoroethyl, benzyl, 2-fluorobenzyl, 2-methylbenzyl or 2-methoxybenzyl.

3. The compound of claim 2, wherein Q represents C-H, C-F, C-Cl or N, R represents hydrogen or amino, R_1 represents cyclopropyl and R_2 represents methyl, t-butyl, homopropargyl, 2-fluoroethyl, benzyl, 2-fluorobenzyl or 2-methoxybenzyl.

4. The compound of anyone of claims 1 to 3, wherein R_3 and R_4 are hydrogen.

5. A process for preparing a quinoline(naphthyridine) carboxylic acid derivative having the following formula (I),



(I)

and its pharmaceutically acceptable non-toxic salt, its physiologically hydrolyzable ester, solvate and isomer, in which

R represents hydrogen, methyl or amino;

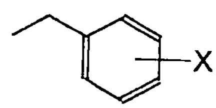
Q represents C-H, C-F, C-Cl, C-OH, $C\text{-}CH_3$, $C\text{-}O\text{-}CH_3$ or N;

R_1 represents cyclopropyl, ethyl, or phenyl which is substituted with one or more fluorine atom(s);

R_2 represents one of the following a) through e):

a) hydrogen, straight or branched C_1-C_4 alkyl, cyclopropyl, cyclopropylmethyl, C_3-C_6 alkynyl, 2-haloethyl, methoxymethyl, methoxycarbonylmethyl, aryl or allyl,

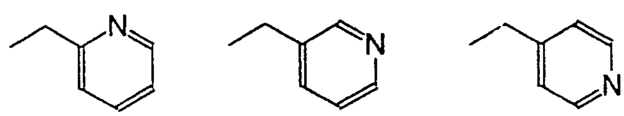
b) a group of the following formula (1),



(1)

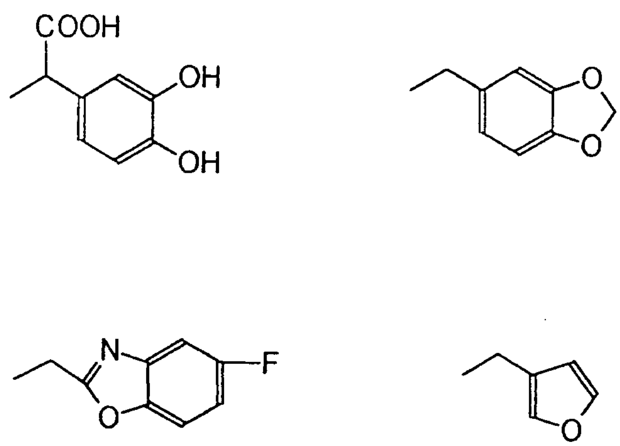
wherein X represents hydrogen, 2, 3 or 4-fluoro, cyano, nitro, methoxy, C_1-C_4 alkyl, or 2,4-difluoro,

c) a group of the following formula (2),



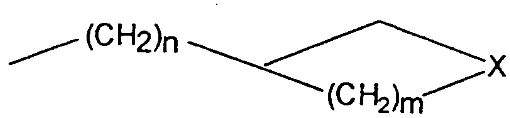
(2)

d) a heteroarylmethyl of the following formula (3),



(3)

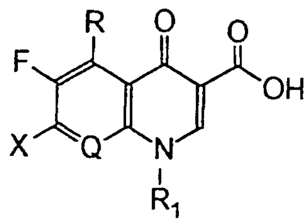
e) a group of the following formula (4),



(4)

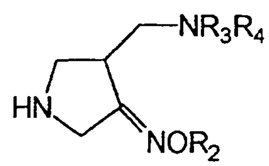
wherein n denotes 0 or 1, m denotes 0, 1 or 2 and X represents methylene, O or N, and

R_3 and R_4 independently of one another represent hydrogen or C_1-C_3 alkyl or R_3 and R_4 together with a nitrogen atom to which they are attached can form a ring, characterized in that a compound having the following formula (II),



(II)

wherein Q, R and R_1 are defined as above and X represents a halogen, is reacted with a compound having the following formula (III),



(III)

wherein R_2, R_3 and R_4 are defined as above, in a solvent in the presence of an acid acceptor.

6. The process of claim 5, wherein the compound of formula (III) is used in the form of a salt with hydrochloric acid, hydrobromic acid or trifluoroacetic acid.

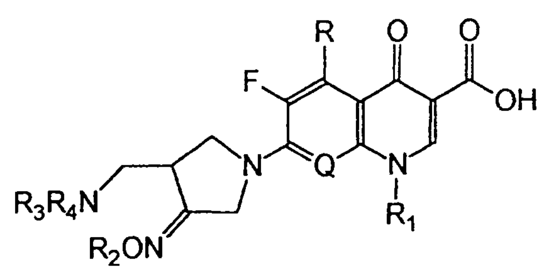
7. The process of claim 5, wherein the compound of formula (III) is used in an equimolar amount to 10 times molar amount with respect to the compound of formula (II).

8. The process of claim 5, wherein said solvent is selected from the group consisting of acetonitrile, dimethylformamide, dimethylsulfoxide, pyridine, N-methylpyrrolidinone, hexamethylphosphoramide, ethanol, and aqueous mixture thereof.

9. The process of claim 5, wherein said acid acceptor is selected from inorganic bases consisting of sodium hydrogen carbonate and potassium carbonate and organic bases consisting of triethylamine, diisopropylethylamine, pyridine, N,N-diemthylaniline, N,N-dimethylaminopyridine, 1,8-diazabicyclo-[5.4.0]undec-7-ene and 1,4-diazabicyclo[2.2.2]octane.

10. The process of claim 5, wherein the reaction is carried out at room temperature to 200°C.

11. A process for preparing a quinoline(naphthyridine) carboxylic acid derivative having the following formula (I),



(I)

and its pharmaceutically acceptable non-toxic salt, its physiologically hydrolyzable ester, solvate and isomer, in which

R represents hydrogen, methyl or amino;

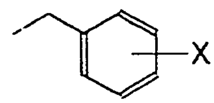
Q represents C-H, C-F, C-Cl, C-OH, $C\text{-}CH_3$, $C\text{-}O\text{-}CH_3$ or N;

R_1 represents cyclopropyl, ethyl, or phenyl which is substituted with one or more fluorine atom(s);

R_2 represents one of the following a) through e):

a) hydrogen, straight or branched C_1-C_4 alkyl, cyclopropyl, cyclopropylmethyl, C_3-C_6 alkynyl, 2-haloethyl, methoxymethyl, methoxycarbonylmethyl, aryl or allyl,

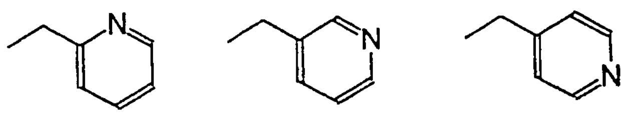
b) a group of the following formula (1),



(1)

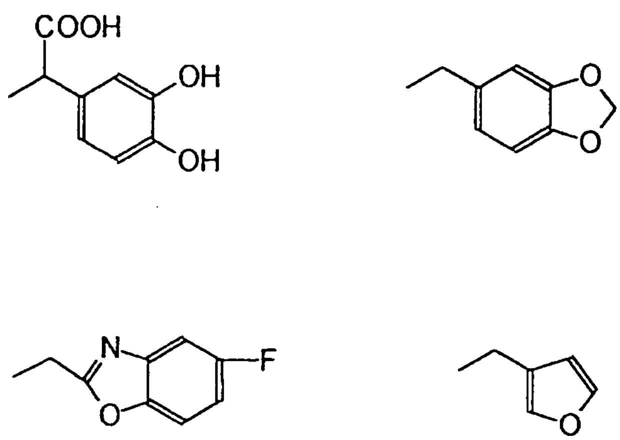
wherein X represents hydrogen, 2, 3 or 4-fluoro, cyano, nitro, methoxy, C_1-C_4 alkyl, or 2,4-difluoro,

c) a group of the following formula (2),



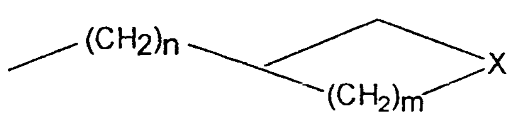
(2)

d) a heteroarylmethyl of the following formula (3),



(3)

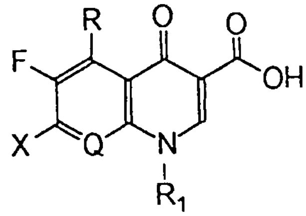
e) a group of the following formula (4),



(4)

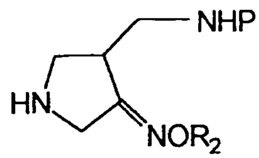
wherein n denotes 0 or 1, m denotes 0, 1 or 2 and X represents methylene, O or N, and

R_3 and R_4 independently of one another represent hydrogen or C_1-C_3 alkyl or R_3 and R_4 together with a nitrogen atom to which they are attached can form a ring, characterized in that a compound having the following formula (II),



(II)

wherein Q, R and R_1 are defined as above and X represents a halogen, is reacted with a compound having the following formula (III'),



(III')

wherein R_2 is defined as above and P is an amino-protecting group, in the presence of a base and then the amino-protecting group P is subsequently removed from the resulting compound.

12. The process of claim 11, wherein the amino-protecting group is formyl, acetyl, trifluoroacetyl, benzoyl, para-nitrobenzoyl, para-toluenesulfonyl, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, benzyloxycarbonyl, para-methoxybenzyloxycarbonyl, trichloroethoxycarbonyl, benzyl, para-methoxybenzyl, trityl or tetrahydropyranyl.

13. An antibacterial composition comprising as an active component the compound of formula (I) as defined in claim 1, together with a pharmaceutically acceptable carrier.

14. The composition of claim 13 comprising 1 to 100mg of the compound of formula (I) in a unit dosage form.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 25 0143

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,Y	EP-A-0 541 086 (KAKEN PHARMACEUTICAL CO., LTD.) * claims 1,5-7 * ---	1,13	C07D401/04 C07D471/04 A61K31/47 //(C07D401/04, 215:00, 207:00), (C07D471/04, 221:00,221:00)
D,Y	PATENT ABSTRACTS OF JAPAN vol. 13 no. 315 (C-619) ,18 July 1989 & JP-A-01 100165 (SHIONOGI & CO LTD) 18 April 1989, * abstract * ---	1,13	
D,Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 35, 1992 pages 1392-1398, C.S. COOPER ET AL. * table I * ---	1,13	
D,Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 34, 1991 pages 1142-1154, J.M. DOMAGALA ET AL. * scheme I, compound I; table II; chart I; tables III-VI * ---	1,13	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
Y	EP-A-0 183 129 (KYORIN PHARMACEUTICAL CO., LTD.) * claims 1,4 * ---	1,13	C07D
A	EP-A-0 266 576 (BRISTOL-MYERS CO.) * table 5, examples 49-51, 84 * * claims 1,21 * ---	1,13	
A	EP-A-0 326 891 (WARNER-LAMBERT CO.) * claims 1,7,11; examples 4,9,17,20 * --- -/--	1,13	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	20 September 1995	Hass, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 25 0143

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A,D	JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, 1988 pages 991-1001, J.M. DOMAGALA * tables II, III * -----	1,13	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	20 September 1995	Hass, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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